Original article

Nutritional risk is associated with long term mortality in hospitalized patients with chronic heart failure

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1. Introduction

Chronic heart failure (CHF) is characterized by high mortality, multiple comorbidities, a complex therapeutic regimen, frequent hospitalization and reduced quality of life [1]. Implementation of guideline-recommended pharmacologic and non-pharmacologic therapies [2] has significantly improved survival among CHF patients, but the mortality rate is still high [3,4]. Known predictors of mortality in patients with CHF are older age [5,6], diabetes [5,6], lower left ventricular ejection fraction (EF) [5,6], higher New York Heart Association classification (NYHA class) [5], elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) [7,8], frailty [9] and cardiac cachexia [10,11]. Observational studies also indicate
that in patients with CHF, the mortality risk increases with lower levels of BMI [5,6,12–14], total cholesterol [13,15] and systolic blood pressure [13]. This inverse relationship between traditional cardiovascular risk factor and mortality in the heart failure patient has been described as “reverse epidemiology” [13].

In addition, poor nutritional conditions have in several studies been strongly associated with mortality in hospitalized patients with CHF [16–19]. At two [16] and three [17,19] years follow up the mortality in CHF patients with a poor nutritional condition has been found to vary between 26.5 and 76%. Furthermore, the prevalence of nutritional risk in hospitalized patients with CHF has been found to vary between 34 and 90% [16–20].

Several screening tools have been designed to assess the patient's nutritional risk, like Mini Nutritional Assessment (MNA), Subjective Global Assessment (SGA), Malnutrition Universal Screening Tool (MUST) and Nutritional Risk Screening (NRS-2002) [21]. The screening tool NRS-2002 was designed and validated by the European Society for Clinical Nutrition and Metabolism (ESPEN) [21,22], and is recommended for use in the hospital setting [21]. NRS-2002 is shown to provide a simple and rapid screening of hospitalized patients [21,22]. ESPEN has described the purpose of nutritional screening as a method “to predict the probability of a better or worse outcome due to nutritional factors, and whether nutritional treatment is likely to influence this” [21, s. 415].

MUST is recommended by ESPEN as a screening tool for the community [21]. The screening tools SGA and MNA are used in hospital settings, but may be more time consuming compared with NRS-2002. In a hospital setting it therefore would be an advantage using NRS-2002 to obtain a rapid and easy screening [21].

NRS-2002 has previously been validated in different hospital settings [23]. Recently, it was evaluated in CHF patients and found adequate to detect nutritional risk in these patients [24]. The predictive validity of nutritional screening tools has often been evaluated against clinical outcome, and especially mortality has been investigated in relation to nutritional risk [25]. In a meta-analysis NRS-2002 has shown fair to good predictive validity to predict inhospital mortality for adults [23]. The association between NRS-2002 and long term mortality (>12 months) is yet to be confirmed in most groups of patients. As far as we know mortality has not been investigated in a CHF sample using the NRS-2002.

The primary objective of this study was therefore to explore the association between nutritional risk assessed with NRS-2002 at admittance to hospital and three-year overall mortality in patients with CHF. In addition we wanted to investigate the association between mortality and the three different components in NRS-2002 (nutritional status, severity of disease and age).

2. Materials and methods

2.1. Design

An observational study with three-year follow-up was performed based on hospitalized CHF patients at St. Olav’s University Hospital in Trondheim, Norway. The recruitment period was between October 2008 and February 2010.

2.2. Participants

CHF was diagnosed according to the recommendation of the European Society of Cardiology [26]. The CHF patients were classified according to the international statistical classification of diseases (ICD-10) for the diagnoses of heart failure (I50) [27]. The following criteria were used to identify hospitalized patients with CHF eligible for the study: 1) directly admitted to the department of cardiology, St. Olav’s University Hospital, 2) age > 18 years, 3) heart failure ≥ 3 months, 4) ejection fraction (EF) ≤ 50% and 5) NYHA classification II, III or IV [28].

In our study a total of 131 patients were included. Fig. 1 (flowcharts) gives a detailed description of excluded patients (N = 157).

2.3. Variables

2.3.1. New York Heart Failure Association classification (NYHA-class)

Heart failure severity was divided into four categories according to the NYHA-classification. NYHA-class I = no symptoms during ordinary physical activity; NYHA-class II = slight limitation during ordinary physical activity; NYHA-class III = marked limitation during ordinary physical activity; NYHA-class IV = inability to carry on any physical activity without discomfort or discomfort at rest [28].

2.3.2. Medication

Information about beta-blockers and angiotensin-converting-enzyme (ACE) inhibitors was obtained from the patient’s records at screening time.

2.3.3. Ejection fraction

Ejection fraction (EF) was measured using cardiac ultrasound (Echocardiography). At the cardiac medical outpatient clinic at St. Olav’s University Hospital all examinations were done by a cardiologist. EF was obtained from the standardized ultrasound result record.

Fig. 1. Flowchart. COPD – chronic obstructive pulmonary disease; EF – ejection fraction.
2.3.4. Blood sample

The day after inclusion, morning serum albumin, pre-albumin, C-reactive protein (CRP) and cholesterol were analyzed. Albumin was analyzed according to standard procedure at St. Olav’s University Hospital [29] using bromocresol green method and the analysis instrument Roche Modular P [29]. Pre-albumin was analyzed by an immunologcal method. Dade-Behring Nephelometer PROSPEC was used as an analytical instrument [29]. CRP was also analyzed with immunlogic method and by the analysis instrument Roche Modular P [29].

2.3.5. Comorbidity

In our study the comorbidity variables were diabetes (yes/no), renal failure with creatinine < 330 µmol/L (yes/no), COPD grade I or II versus no, and hypertension (yes/no).

2.3.6. Anthropometry

In the morning, before breakfast, the patients were weighed without shoes with light clothes on a portable Seca digital scale to the nearest 0.1 kg. The weight was standardized and controlled. Height was measured with Seca stadiometer to the nearest cm. The following formula was used to calculate body mass index (BMI):

\[
BMI = \text{weight (kg)} / \text{height (m)}^2 \quad [30].
\]

2.3.7. Weight loss

Percent weight loss was estimated using the formula:

\[
(\text{weight loss/earlier weight}) \times 100 = \text{weight loss in \%}.
\]

Self-reported weight was used to calculate percentage weight loss.

2.3.8. Nutritional screening

According to Kondrup et al. [21,22], the nutritional risk score in NRS-2002 is based on an evaluation of the following three components: nutritional status, severity of disease and age. The patients are given a score from 0 to 3 for nutritional status, and from 0 to 3 for the severity of disease. A score of 1 is added to patients 70 years and older. The total score is from 0 to 7, and if the sum score is 3 or more, the patient is classified at nutritional risk by NRS-2002. Nutritional status in NRS-2002 is evaluated by three individual components: BMI, recent weight loss (≥ 5% within the last 1, 2 or 3 months) and food intake the preceding week. Information about food intake during the week prior to admission was obtained by a special nurse (trained by a dietitian), using an interview with the patient. The questions focusing on food intake prior to hospitalization were compared with normal intake. Furthermore, the food intake was categorized into 0–25%, 25–50% and 50–75% of normal requirement [21,22]. The inter-rater reliability of NRS-2002 between the trained special nurse and a dietitian was documented to be substantial with a kappa value of 0.81 in our previous published work [24].

In our study the scoring system of severity of disease was based on the patient’s NYHA-classification [28] and Kondrup et al.’s prototype of score 1, 2 or 3 on severity of disease [22, s. 330]. Patients in NYHA-class II or III had a reduced state of health, but were regularly out of bed and received score 1. Most of the patients in NYHA-class IV were confined to bed due to illness and received score 2. Score 3 should be given to patients in NYHA-class IV and in need of intensive care treatment.

2.3.9. Nutritional intervention

During the hospital period we registered the nutritional treatment the patient received such as oral nutritional supplements, enteral tube feeding or parenteral nutrition which were documented in the hospital record. In addition we registered if a patient had received ICD-10 code for mild, moderate or severe malnutrition (E43, E44.0, E44.1) in the discharge summary.

2.3.10. Mortality

In Norway all deaths are registered in a central Cause of Death registry. The registry is complete. Data are transferred electronically to the hospital administrative system based on the national 11 digit identity number. Deaths both in and out of hospital are registered. Survival was confirmed through the Norwegian Cause of Death Registry.

2.4. Procedure

Informed written consent was obtained from each patient. Within 72 h of admission nutritional screening was performed using the NRS-2002. The nutritional screening with NRS-2002 and the measurements of weight and height was completed by one investigator (KT). Time of death was obtained from all participants during the three-year (1095 days) follow-up (KT).

The Regional Research Ethics Committee and the Norwegian Social Science Data Services approved the study.

2.5. Statistical analysis

The data was analyzed with SPSS, version 22. Results were considered significant when \( P < 0.05 \). Normally distributed continuous data were analyzed by two-tailed independent t-test. The remaining independent continuous data were analyzed by Mann–Whitney U Test. Categorical data were analyzed by the Chi-Square Test or by the Fisher Exact test (depending on sample size).

All participants were followed for three years (1095 days) after nutritional screening with NRS-2002. Kaplan–Meier survival curves describing three-year mortality were obtained for the two groups according to the NRS-2002 classification (NRS-2002 < 3 versus NRS-2002 ≥ 3). In addition we used Kaplan–Meier survival curves to investigate the association between three-year mortality, nutritional status (score 0 versus score 1, 2 or 3 on nutritional status) and the three individual nutritional components in NRS-2002 (food intake > 75% versus ≤ 75% of normal requirement in the preceding week, weight loss < 5% versus ≥ 5% last 1–3 months and BMI > 20.5 versus BMI ≤ 20.5). Log Rank (Mantel–Cox) was used to test the mortality differences between the groups presented in the Kaplan–Meier survival curves.

Mortality was first studied using binary logistic regression analysis (the ‘Enter’ method) in order to estimate the risk of three-year mortality (yes/no). In the bivariate analysis the independent variables NRS-2002, gender, EF, beta-blocker, ACE-inhibitor, albumin, pre-albumin, CRP, cholesterol and comorbidity (diabetes, renal failure with creatinine < 330 µmol/L, COPD grade I or II, hypertension) were studied. The independent variables with \( P < 0.2 \) were included in the final multivariate model. Results are presented as odds ratio (OR) with confidence intervals (CI) of 95%.

Thereafter, the time to death was studied using Cox proportional hazard regression analysis. This analysis takes into account both the importance of baseline vital status and the time before the event occurs. The same initial independent variables, the same reference levels and the same assumptions for inclusion in further analyses were used in this assessment method as in the logistic regression analyses. In addition, the three components of NRS-2002 (score of nutritional status, severity of disease and...
age) were also explored in unadjusted and adjusted analyses and finally chosen in the presented adjusted analyses rather than the sum-score of NRS-2002. The results are given in hazard ratios (HR) with CI of 95%.

The association between nutritional status (component in NRS-2002), severity of disease (component in NRS-2002), inflammation and the patient hydration status and the outcome variable albumin (< 34 g/L) was investigated with logistic regression analysis (the “Enter method”). As an indication of inflammation a CRP cut-off value of 10 was chosen [31] and indicators for hydration status were peripheral edema, ascites and congestion on chest X-ray.

### 3. Results

#### 3.1. Characteristics of the study sample

The study sample consisted of 131 patients, 42 (32.1%) were women. The median age was 78 years, range 37–95. 16% of the patients were classified in NYHA-class II, 64.1% in NYHA-class III and 19.9% in NYHA-class IV. In all, 80% of the patients used beta-blockers and 82% ACE-inhibitors at the time of screening.

The group of excluded patients (N = 157) had a similar gender distribution (48.3% women), but they were older (median 82 years versus 78 years, P < 0.05) and had higher mortality during follow-up (104 of 157 patients) than the patients in the study sample (69 of 131 patients) (P < 0.05). Adjusted for age, excluded patients did not have significant higher odds for mortality compared to included patients (OR 1.42; 95% CI 0.83–2.46, P = 0.205).

The prevalence of nutritional risk according to NRS-2002 (score ≥ 3) was 57.3% (75 of 131 patients). All patients were weighted in light clothing on a Seca digital scale at the time of the initial screening. Table 1 shows the characteristics for non-risk patients (NRS-2002 < 3) and risk patients (NRS-2002 ≥ 3) at screening time. Four of 75 patients at nutritional risk received oral nutritional supplements. None of the patients were treated with tube feeding or parenteral nutrition. In the discharge summary none of the patients had an ICD-10 code for mild, moderate or severe malnutrition.

#### 3.2. Prevalence and factors associated with three-year mortality

In all, 69 (52.6%) of the included patients died within the period of three-year follow-up (Table 2).

Totally within three-year follow up more patients at nutritional risk died (N = 51) compared to patients not at risk (N = 18), P = 0.001 (Table 2). Mortality by year is presented in Table 2 and the Kaplan–Meier survival curves are shown in Fig. 2 (Log rank test Mantel Cox), Chi Square 18.40, P < 0.001. Fig. 3a–d presents the association between mortality and nutritional status and the three individual components of nutritional status in NRS-2002.

In the adjusted logistic regression analysis the odds for three-year mortality was more than five-fold higher in patients with NRS-2002 ≥ 3 (OR 5.85; 95% CI 2.10–16.24) (Table 3).

### Table 1

| Characteristics of patients with NRS-2002 < 3 versus NRS-2002 ≥ 3 (N = 131). |
|---------------------------------|-----------------|-----------------|
|                                 | NRS-2002 < 3    | NRS-2002 ≥ 3    | P     |
| Demographics:                  |                |                |       |
| Age (year) Median              | 70.5            | 81              | <0.001*** |
| Women                          | 14 (33.3)       | 28 (66.7)       | 0.135b |
| Men                            | 42 (47.2)       | 47 (52.8)       | 0.135b |
| Nutritional status:            |                |                |       |
| Food intake ≤ 75%              | 1 (2.2)         | 44 (97.8)       | <0.001***d |
| Weight loss ≥ 5%               | 0               | 11 (100)        | 0.002* |
| BMI ≤ 20.5 (kg/m²)             | 0               | 15 (100)        | <0.001***d |
| Heart failure status:          |                |                |       |
| NYHA-class II                  | 18 (85.7)       | 3 (14.3)        | <0.001***b |
| NYHA-class III                 | 36 (42.4)       | 49 (57.6)       |       |
| NYHA-class IV                  | 2 (8.0)         | 23 (92)         |       |
| EF (%) Median                  | 33              | 30              | 0.015a |
| Beta-blocker                   | 42 (40.0)       | 63 (60.0)       | 0.201b |
| ACE-inhibitor                  | 46 (43.0)       | 61 (57.0)       | 0.906b |
| Congestion chest X-ray         | 29 (34.5)       | 55 (65.5)       | 0.077b |
| Ascites                        | 0 (0)           | 3 (100)         | 0.260f |
| Peripheral edema               | 29 (40.8)       | 42 (59.2)       | 0.632b |
| Biochemical:                   |                |                |       |
| Albumin (g/L) Mean             | 38.8 (3.3)      | 35.6 (4.2)      | <0.001***c |
| Pre-albumin (g/L) Mean         | 0.21 (0.56)     | 0.17 (0.62)     | <0.001***c |
| CRP (mg/L) Median              | 9.5             | 26              | <0.001***a |
| Cholesterol (≥ 5.5 mmol/L)     | 4 (66.7)        | 2 (33.3)        | 0.401d |
| Co-morbidity:                  |                |                |       |
| Renal failure eGFR < 30 ml/min | 10 (33.3)       | 20 (66.7)       | 0.235b |
| Diabetes                       | 19 (50.0)       | 19 (50.0)       | 0.284b |
| COPD degree I/II               | 8 (44.4)        | 10 (55.6)       | 0.876b |
| Hypertension                   | 22 (44)         | 28 (56)         | 0.820b |

NRS-2002 – nutritional risk screening; EF – ejection fraction; NYHA – New York Heart Association; CRP – C-reactive protein; COPD – chronic obstructive pulmonary disease.

*p < 0.05.

***P < 0.001.

a Significance testing with Mann Whitney U test.

b Significance testing with Chi-square test.

c Significance testing with Independent T Test.

d Significance testing with Fisher Exact Test.

e Food intake ≤ 75% the preceding week.

f Weight loss ≥ 5% last 1–3 month.
In the Cox proportional hazard regression analyses adjusted for gender, beta-blocker, ACE-inhibitor, albumin and renal failure, NRS-2002 was associated with increased mortality (HR 2.78; 95% CI 1.53–5.03). The association between mortality and the three components of NRS-2002 (poor nutritional status, high severity of disease and age ≥ 70 years) was also studied in adjusted hazard regression analyses (Table 4). The analyses showed that poor nutritional status (HR 1.82; 95% CI 1.03–3.22), high severity of disease (NYHA-class IV) (HR 1.78; 95% CI 1.00–3.16) and age ≥ 70 years (HR 3.24; 95% CI 1.48–7.10) were associated with mortality. Including age as a continuous variable in the adjusted analysis, the coefficients for nutritional status and severity of disease did not change. HR (95% CI) for three year mortality was for age per year 1.06 (1.03–1.09; P < 0.001).

Cox proportional hazard regression analyses were also used to examine the association between mortality and the individual components of nutritional status in NRS-2002. The analysis was adjusted for the same independent variables as presented in Table 4. HR (95% CI) for three year mortality was for food intake (≤ 75% of normal requirement in the preceding week) 1.35 (0.72–2.51; P = 0.345), for weight loss (≥ 5% last 1–3 months) 2.66 (1.09–6.48; P = 0.031), and for BMI < 20.5 5.25 (2.23–12.35; P < 0.001). All Cox proportional hazard regression analyses were adjusted for level of albumin (< 34 g/L or not), which was independently associated with increased mortality.

In the supplementary adjusted logistic regression analysis of low albumin (< 34 g/L), neither CRP (cut-off 10 mg/L), congestion on chest X-ray, ascites, peripheral edema or severity of disease (NYHA-class IV) were associated with the outcome, only the nutritional component of NRS-2002 (OR 1.81; 95% CI 1.12–2.93; P = 0.015) was associated with low albumin.

**4. Discussion**

In the present study, 131 hospitalized patients with CHF were evaluated for nutritional risk by NRS-2002. The prevalence of nutritional risk was 57%. Nutritional risk defined by NRS-2002 was an independent risk factor predicting three-year mortality in adjusted analyses. The three components in NRS-2002 (nutritional status, severity of disease, age) were all independently associated with higher mortality.

**4.1. Nutritional risk and mortality in chronic heart failure patients**

The prevalence of nutritional risk in hospitalized patients with CHF has in studies differed from 34 to 90% [16–20], partly due to methodological differences, the screening tool used and groups of patients assessed. Thus, the prevalence of nutritional risk in the present sample is in the range of previous studies. To our knowledge this is the first study using NRS-2002 to investigate the association between nutritional risk and long-term mortality in hospitalized patients with CHF. In our study, the mortality rate was significantly higher in patients at nutritional risk than in patients not at nutritional risk.

In bivariate analyses, we found that patients at nutritional risk had increased mortality mainly during the first year after discharge from hospital. These results indicate that CHF patients at nutritional risk are a very vulnerable patient group. We included mostly very old patients, thus, three years may be a long follow up time, and may also partly explain the high mortality within one year in this analysis.

Furthermore, in adjusted analyses we found that CHF patients at nutritional risk (NRS-2002 ≥ 3) had more than five-time higher risk of death during three-year follow up than non-risk patients. Moreover, in Cox multivariate analysis where time to death was taken into consideration, the CHF patients at nutritional risk were more likely to die prior to those not being at nutritional risk in the three-year follow-up period also after adjusting for co-morbidity variables and gender. In line with our result, three previous studies exploring the impact of poor nutritional conditions on mortality in hospitalized CHF patients, found that poor nutritional condition was an independent predictor of longterm mortality [two and three year] [16–18]. In total 68% of the CHF patients at nutritional risk had died during three years follow up and this is in the upper range of previous studies where the mortality was found to be between 26.5–42% [17] and 35.9–76% [16] in CHF patients with a poor nutritional condition (including the components at “nutritional risk” and “malnourished”). However, these studies...
used the MNA [16,17] and not NRS-2002. Furthermore, Aggarwal et al. [17] investigated the nutritional condition in a sample of patients with decompensated advanced heart failure. We included CHF patients with either decompensated or compensated chronic heart failure, and our sample may therefore not be fully comparable with Aggarwal et al.'s sample of severe heart failure patients [17]. Our sample is to a greater extent comparable with Bonilla-Palomas et al.'s study [16]. They included both decompensated and compensated patients with CHF. Furthermore, CHF patients in their study were diagnosed according to the recommendation of the European Society of Cardiology [26], which is in line with diagnostic criteria used in our study.

According to the results in our study, we can conclude that NRS-2002 is a non-invasive and inexpensive tool to be recommended as part of routine nutrition screening of CHF patients at hospital admittance. The high prevalence of nutritional risk and three-year mortality rate in this patient group, indicate that early identification of CHF patients at nutritional risk and implementation of nutritional support are relevant to prevent malnutrition [21,22]. Whether nutritional support has effect on clinical outcome in CHF patients at nutritional risk are, however, still unknown [32]. In our study none of the risk patients were diagnosed with malnutrition (mild, moderate or severe) in the discharge summary, and only four of the patients at nutritional risk, according to the records, received nutritional support (oral nutritional supplements). When this present study was conducted, nutritional screening was not a routine in our department at St. Olav’s Hospital. It has been shown that in the absence of a formal screening procedure, malnourished patients tend to be both under diagnosed and under treated [33,34]. This could possibly explain why none of the risk patients in our sample were diagnosed and why so few patients at nutritional risk received nutritional treatment. However, we cannot rule out the possibility that some patients were given oral nutritional supplements without it being recorded. Nevertheless, our results emphasize the need for systematic nutritional screening of CHF-patients. Nutritional risk has to be identified before it can be treated. Since the mean hospital stay is short for CHF patients [24] it is important that the patients, community or another institution

Fig. 3. a–d: Kaplan–Meier plot: Days of survival up to three years (1095 days). a–d presents the association between mortality, nutritional status and the three individual components of nutritional status in NRS-2002. a: Normal nutritional status (score 0) versus score 1, 2 or 3 on nutritional status in NRS-2002. Log rank test (Mantel Cox), Chi Square 10.243, *P < 0.001. b: Food intake > 75% versus \( \leq 75\% \) of normal requirement in preceding week. Log rank test (Mantel Cox), Chi Square 0.00, *P = 0.985. c: Weight loss < 5% versus \( \geq 5\% \) last 1–3 months. Log rank test (Mantel Cox), Chi Square 2.757, *P = 0.097. d: BMI > 20.5 versus \( \leq 20.5 \). Log rank test (Mantel Cox), Chi Square 24.012, *P < 0.0001.
Table 3
Relationship between three years mortality and nutritional risk (NRS-2002 ≥ 3 versus not) in unadjusted and adjusted logistic regression analyzes.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted LRA</th>
<th>Adjusted LRA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>NRS-2002 ≥ 3</td>
<td>4.49</td>
<td>2.14–9.42</td>
</tr>
<tr>
<td>Gender (man)</td>
<td>0.58</td>
<td>0.27–1.22</td>
</tr>
<tr>
<td>EF ≤ 30%</td>
<td>0.59</td>
<td>0.30–1.18</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>1.93</td>
<td>0.79–4.71</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>4.33</td>
<td>1.51–12.45</td>
</tr>
<tr>
<td>Albumin &lt; 34 g/L</td>
<td>5.43</td>
<td>2.05–14.40</td>
</tr>
<tr>
<td>Pre-albumin &lt; 0.26 g/L</td>
<td>1.26</td>
<td>0.48–3.34</td>
</tr>
<tr>
<td>CRP &gt; 10 mg/L</td>
<td>1.50</td>
<td>0.65–3.45</td>
</tr>
<tr>
<td>Cholesterol ≥ 5.5 mmol/ml</td>
<td>0.89</td>
<td>0.17–4.60</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4.98</td>
<td>1.87–13.22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.09</td>
<td>0.54–2.21</td>
</tr>
</tbody>
</table>

LRA = logistic regression analyzes; OR = odds ratio; CI = confidence interval; NRS-2002 = nutritional risk screening; CRP = C-reactive protein; COPD = chronic obstructive pulmonary disease; ACE = angiotensin-converting-enzyme.

*P < 0.05.
**P < 0.01.
***P < 0.001.

a Unadjusted logistic regression analyzes. Independent variables included separately. Dependent variable: Three years mortality. Independent variables: NRS-2002 (score < 3 reference category), gender (woman reference category), EF (> 30% reference category), beta-blocker, ACE-inhibitor, albumin (≥ 34 g/L reference category), pre-albumin (≥ 0.26 g/L reference category), cholesterol (≤ 5.5 mmol/ml reference category), renal failure with creatinine < 330 μmol/L, diabetes, COPD degree I/II, hypertension.

b Adjusted logistic regression analysis. The variables included in the unadjusted analyzes with P < 0.20 were used.

Table 4
Adjusted hazard ratio (Cox multivariate analysis) for overall three year mortality in the study sample (N = 131).

<table>
<thead>
<tr>
<th></th>
<th>Crude HR (95% CI)</th>
<th>P</th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS-2002 ≥ 3</td>
<td>3.09 (1.79–5.27)</td>
<td>&lt;0.001***</td>
<td>1.82 (1.03–3.22)</td>
<td>0.039*</td>
</tr>
<tr>
<td>Nutritional status</td>
<td>2.28 (1.38–3.76)</td>
<td>0.002**</td>
<td>1.78 (1.00–3.16)</td>
<td>0.047*</td>
</tr>
<tr>
<td>Severity of disease</td>
<td>1.85 (1.09–3.20)</td>
<td>0.029*</td>
<td>3.24 (1.48–7.10)</td>
<td>0.003**</td>
</tr>
<tr>
<td>Age ≥ 70 year</td>
<td>5.05 (2.41–10.59)</td>
<td>&lt;0.001***</td>
<td>0.77 (0.44–1.33)</td>
<td>0.345</td>
</tr>
<tr>
<td>Gender (man)</td>
<td>0.70 (0.43–1.14)</td>
<td>0.153</td>
<td>2.14 (1.17–3.94)</td>
<td>0.014*</td>
</tr>
<tr>
<td>EF &gt; 30%</td>
<td>0.77 (0.48–1.23)</td>
<td>0.274</td>
<td>1.67 (0.92–3.02)</td>
<td>0.089</td>
</tr>
<tr>
<td>β-blocker</td>
<td>1.51 (0.88–2.62)</td>
<td>0.151</td>
<td>2.05 (1.21–3.47)</td>
<td>0.007**</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>2.30 (1.35–3.90)</td>
<td>0.003**</td>
<td>3.16 (1.48–7.01)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Albumin &lt; 34 g/L</td>
<td>3.04 (1.84–5.00)</td>
<td>&lt;0.001***</td>
<td>1.71 (0.93–3.13)</td>
<td>0.083</td>
</tr>
<tr>
<td>Pre-albumin &lt; 0.26 g/L</td>
<td>1.18</td>
<td>0.58–2.38</td>
<td>0.646</td>
<td></td>
</tr>
<tr>
<td>CRP &gt; 10 mg/L</td>
<td>1.32 (0.76–2.32)</td>
<td>0.330</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol ≥ 5.5 mmol/ml</td>
<td>0.72</td>
<td>0.23–2.29</td>
<td>0.576</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>2.33 (1.41–3.83)</td>
<td>&lt;0.001***</td>
<td>1.71 (0.93–3.13)</td>
<td>0.083</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.19 (0.72–1.97)</td>
<td>0.502</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD degree I/II</td>
<td>1.34 (0.72–2.49)</td>
<td>0.361</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.99 (0.61–1.62)</td>
<td>0.986</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval; NRS-2002 = nutritional risk screening; EF = ejection fraction; ACE = angiotensin-converting-enzyme; CRP = C-reactive protein; COPD = chronic obstructive pulmonary disease.

*P < 0.05.
**P < 0.01.
***P < 0.001.
BMI and weight loss in CHF patients may be due to low protein and energy intake, malnutrition and cardiac cachexia [12]. In our study all patients with either low BMI (15 of 131) or weight loss (11 of 131) were classified at nutritional risk (NRS-2002 ≥ 3). Furthermore, we found in adjusted analysis that patients with high severity of their heart failure (NYHA class IV versus not) had almost double the risk for mortality as those with less serious severity of the disease. The present result is consistent with previous studies of CHF patients that have found that higher NYHA-class was associated with two-year [5] and three-year [6] mortality. However, baseline assessment in these studies was not conducted in hospitalized patients.

High age (≥ 70 years) increased the risk for mortality more than threefold. Age per year was also associated with three year mortality. In previous studies age has also been shown to be a powerful predictor of mortality in patients with CHF [5,6].

In addition, hypoalbuminemia was associated with higher mortality in our sample. Other studies have found an evident association between hypoalbuminemia and mortality in CHF patients [36,37]. Use of albumin may add valuable information of association between hypoalbuminemia and mortality in CHF patients. We did not find an association between nutrition and albumin for mortality. The serum protein pre-albumin has a half-life of 48 h [38] and may reflect a more recent picture of the patient’s nutritional condition [38]. It could be of value to measure albumin and pre-albumin routinely as part of the clinical assessment of the CHF patients. We did not find an association between pre-albumin at inclusion and three-year mortality. A previous study has found a significant association between low discharge pre-albumin (≤ 15 mg/dl) and 6 months mortality in hospitalized heart failure patients [39]. Unfortunately, we did not have any discharge measures.

4.2. NRS-2002 and long term predictive value

Thus, nutritional risk assessed with NRS-2002 had importance for long-term mortality in patients with CHF. As previously mentioned, the results from the present study are quite consistent with other studies of CHF patients using other screening tools. In addition our results are consistent with studies using NRS-2002 to study the association between mortality and samples of hospitalized patients in general [35,40]. However, the studies of general samples of hospitalized patients had shorter follow up period, i.e. 6 months [40] and 12 months [35]. A small study conducted by Holst et al. [25] in elderly hospitalized patients with a wide range of diagnoses, did not find an association between nutritional risk and 12 month mortality. Thus, the results are somewhat inconsistent. Further studies are needed to clarify and support our findings according to long term mortality in hospitalized patients with CHF and also in other hospitalized patient groups using NRS-2002.

4.3. Strengths and limitations

According to Van Bokhorst-de van der Schueren [23] clinical outcomes are influenced by factors other than nutritional status alone. The author argues that clinical studies investigating the importance of nutritional status, are of less value if they have not adjusted for factors such as age, severity of disease and diagnoses [23]. Therefore, a strength of our study is that we have adjusted for these factors and other comorbidity variables when we investigated the association between the component of nutritional status in NRS-2002 and mortality. We find it likely that nutritional status has a separate influence on clinical outcome in patients with CHF as found in the present study.

Another strength of our study is that we have information on when all included patients died due to a complete Norwegian Cause of Death Registry. Furthermore, no participant was lost to follow-up.

However, there are several limitations to address. Firstly, the study has a limited sample size. Low sample size limits statistical power. Furthermore, the study was a single center study with a somewhat selected sample (Fig. 1). Thus, the results should be interpreted with caution.

Secondly, a limitation of our study is the heterogeneous sample according to age and severity of disease, which are two key factors for mortality in patients with CHF [5,6]. The age range (37–95 years) is large. Since we included both uncompensated and compensated patients with CHF, we also had a wide range in the severity of disease (NYHA classification from II to IV). Thus, even if, poor nutritional status, was adjusted for severity of disease, we cannot rule out the possibility of rest confounding due to the sample heterogeneity.

Thirdly, frailty [9], functional decline, social isolation and declined cognitive function may influence the mortality rate in elderly persons [41]. However, we were not able to adjust for these factors. Frailty is probably also related to poor food intake. In addition we could not adjust for NT-proBNP, a known predictor of mortality in patients with CHF [7]. Even so, we think it is unlikely that this have affected the relationship between nutritional risk and mortality, because NT-proBNP is strongly associated with the severity of heart failure (NYHA-classification) [8,42], which is adjusted for in the analyses.

Fourthly, inflammation and hydration factors associated with low plasma level of albumin, is of interest to better understand the importance of albumin in the present study. A measure of hemoglobin, hematocrit, sodium and osmolality in serum would have been better indicators for the patient hydration status [43] than we used, but unfortunately we do not have such information.

Fifthly, the analyses would have been more powerful if nutritional screenings were done at regular intervals during the hospital stay and at discharge. Unfortunately the nutritional screening was just done at baseline. In addition, our assessment of disease severity was based on the patients NYHA-classification [28] and with Kondrup et al.’s prototype of score on severity of disease [22]. This scoring system is not validated in patients with CHF, and needs further investigation.

Lastly, we used one screening tool for evaluating the nutritional risk of hospitalized patients with CHF. A comparison of the results using another screening tool, e.g. MNA, SGA and MUST [21] could have increased the impact of our study.

5. Conclusion

In summary, the results of the present study show a high prevalence of nutritional risk (NRS-2002 score ≥ 3) in hospitalized patients with CHF. The nutritional risk state as defined by NRS-2002 was associated with increased mortality and was an independent predictor of three-year mortality in multivariate analysis. Poor nutritional status, high severity of disease, and high age (≥ 70 years), i.e. all components in NRS-2002, were independently associated with mortality. Screening of nutritional risk should therefore be integrated as a part in the overall assessment of hospitalized patients with CHF.
Statement of authorship

KT carried out the study and data analyses and drafted the manuscript. HT gave statistical advice and drafted the manuscript. MIH participated in the data collection and helped to draft the manuscript. AKS participated in the study design, gave statistical advice and drafted the manuscript. All authors have read and approved the final manuscript.

Conflict of interest statement

There is no financial conflict of interest for any of the authors.

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