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Relationship of anemia and clinical outcome in heart failure patients with preserved versus reduced ejection fraction in a rural area of Thailand

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ABSTRACT

Background: Heart failure (HF) has become a significant health burden in developing countries where anemia is highly prevalent. Limited data exists on the effects of anemia on HF in these population.
Methods: A retrospective observational study was conducted in all adult patients hospitalized due to HF at Buriram Hospital in Thailand, during July 2010 to June 2015. Survival analysis was performed to evaluate the impact of anemia on 1- year all-cause mortality for the overall cohort, patients with HF with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF).
Results: A total of 414 HF patients including 287 HFpEF patients (69.3%) and 127 HFrEF patients (30.7%) were included in our analysis. Mean age was 62.51 ± 14.89 years, with 55% female. Overall prevalence of anemia in HF was 62.6% (259 patients). One-year all-cause mortality was significantly higher in patients with anemia than in non-anemia groups (20.08% vs 12.26%, p = 0.041). When analyzed based on types of HF, anemia significantly increased mortality risk in HFpEF group [adjusted hazard ratio (HR) 2.667, 95%CI, 1.216–5.853, p = 0.014] but not with HFrEF group (adjusted HR 0.901, 95%CI, 0.376–2.155, p = 0.804). The mortality of anemic patients who were left untreated was significantly higher than those who were treated (adjusted HR 2.13, 95%CI, 1.13–3.99, p = 0.027).
Conclusion: Anemia significantly increased mortality in HF patients, especially among HFpEF. Attempts to identify, diagnose and manage anemia should be integrated in HF care plan in developing countries with high prevalence of anemia.

1. Introduction

Heart failure (HF) is a common cardiac disease affecting 26 million people around the world [1]. A recent international survey suggested that 1 year all-cause mortality rate for hospitalized and stable ambulatory HF patients were 17% and 7%, respectively [2]. Prevalence of HF varies widely depending upon geographic variation [1]. The potential explanation is thought to be from the difference of HF characteristics for each region including etiologies of HF, comorbidities, and healthcare system [1,3,4]. Recent studies suggested that HF prevalence has been continuously increasing worldwide [5]. HF has now become an important health problem in developing countries with significant healthcare burden to society [3,6–9]. For Thailand, HF is currently one of the leading causes of hospitalization [10]. The number of acute heart failure or decompensated heart failure has increasing annually with number of HF admission of 171,125 in 2013 to 201,914 in 2017 [10].

Comorbidities are crucial factors affecting prognosis of HF. A number of diseases have been shown to increase morbidity and mortality in patients with HF [11]. Among these comorbidities, anemia has been shown to increase mortality and hospitalization, impair health-related quality of life, and reduce exercise capacity among patients with HF. Hypoxic condition due to anemia requires hemodynamic compensation involving a vasodilation-mediated high-output state with neurohormonal activation and ultimately leads to worsening prognosis of HF [12–14]. Data from the Western population showed that anemia increased mortality in patients with HF irrespective of ejection fraction [15]. However, the majority of the data were derived from patients with HF with

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reduced ejection fraction (HFrEF) despite the fact that 50% of HF population had preserved ejection fraction (HFpEF) [15]. A recent large prospective, multinational study among Asian countries including Thailand showed very high incidence of anemia in HF patients (30–50%) and anemia adversely impacts quality of life and survival [16]. Moreover, results of the study also suggested differential effect on morbidity and mortality among different Asian ethnic groups [16]. This implies that a specific study for a specific ethnicity or country may be useful. We therefore aimed to evaluate the effect of anemia on morbidity and mortality in patients with HF. We also compared influence of anemia on HF prognosis between HFrEF and HFpEF.

2. Methods

2.1. Study design and subjects

A retrospective cohort study was conducted among HF patients admitted to the Buriram Hospital, a 900-bed, public, tertiary-care hospital in Thailand under the Ministry of Public Health, during July 2010 - June 2015. The hospital provides medical care to over 1,500,000 persons living in Buriram province and its vicinity. Buriram province is situated approximately 380 km away from Bangkok, the capital city of Thailand. The province is located in the lower northeast part of Thailand bordering Cambodia with an average annual income of 1,830 USD/person/year. There are approximately 70,000 hospital admissions and 650,000 outpatient visits annually to the hospital. Attending patients have a permanent and personal registration number in the hospital, which allows accurate and complete collection of patient's hospital visits, both for outpatient visits and hospital admissions. These data were documented into the central computerized database system and served as our data source. For this study, all Thai adult patients hospitalized with the principal diagnosis of HF was identified by the International Classification of Disease, Tenth Revision (ICD-10) (I50: Heart failure, I50.0: Congestive heart failure, I50.1: Left ventricular failure, I50.9: Heart failure, unspecified). Patients were categorized into 2 groups; those with anemia and those without anemia. The presence of anemia was based on the World Health Organization (WHO) criteria. Anemia was defined by having hemoglobin (Hb) of < 13.0 g/dL for men and < 12.0 g/dL for women. Patients were further categorized based on their ejection fraction (EF) into HFrEF (ejection fraction of $\leq$ 40%) and HFpEF (ejection fraction of $\geq$50%, having either non-dilated left ventricle with concentric remodeling or left ventricular hypertrophy and left atrial enlargement). Patients were excluded if they met any exclusion criteria; age < 18 years, missing critical data (Hb values and ejection fraction), transferred to other hospitals, referral patients without longitudinal follow-up information and loss to follow-up. The study protocol was approved by the Research Committee at Buriram Hospital (BR0032.102.3/297) and Mahidol University Institutional Review Board (MU-DT/PY-IRB No 2016/055.0510) in 2016.

2.2. Data collection

After the study cohort had been identified, data were extracted from hospital database using a structured case record form. Manual chart reviews were also conducted and relevant data were extracted when necessary. Demographic data of patients including age, sex, medical history, relevant and laboratory tests were collected. EF value was collected from echocardiography report during the admission. In case where there was no echocardiography performed during the admission, the EF within 3–6 months prior or after admission was used. Heart failure medications on admission along with therapies for anemia employed during follow-up such as iron supplement, folic acid, oral vitamin B12, erythropoiesis stimulating agent, and blood transfusion were also collected.

2.3. Outcomes of interest

The primary outcome of interest was 1-year all-cause mortality among HF patients with and without anemia. The relationship between anemia and clinical outcome were subsequently evaluated in HFrEF compared to HFpEF. Secondary outcomes were time to mortality, time to re-hospitalization, and length of stay (LOS).

2.4. Statistical analysis

Qualitative variables were tabulated as frequencies and percentages (%) and continuous variables as means ± SD. Continuous variables were tested for normality by the Kolmogorov-Smirnov test. Baseline characteristics and clinical outcomes were compared between groups using the student's *t*-test for continuous variables and Pearson's chi square test for categorical variables. Survival analysis was assessed using the Kaplan-Meier methods. Differences between the survival curves were evaluated by log-rank statistic. Kaplan-Meier curves and log-rank test were used to describe time to events and compare the outcomes. COX regression model was performed to assess the hazard ratio (HR) of all-cause mortality associated with anemia. Covariates included in Cox model were baseline age, gender, smoking status, use of angiotensin converting enzymes or angiotensin receptor blockers, (ACEI/ARB), use of beta-blockers and hypertension. To comprehensively capture the effects of other comorbidities, we incorporated the Charlson Comorbidity Index (CCI) into the regression model [17]. The alpha value of $p \leq 0.05$ was chosen to determine statistical significance. The 95% confidential intervals (CIs) were calculated. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0.

3. Results

From a total of 889 patients living inside the hospital's insurance coverage who were admitted with the diagnosis of HF, 475 patients were excluded. Reasons for exclusion were lack of LVEF data (242 patients), being transferred to other hospitals (92 patients), loss to follow (84 patients), age < 18 years (41 patients) and lack of hemoglobin values during admission (6 patients), suffering from thalassemia (6 patients) and with moderate to severe rheumatic heart disease (4 cases). There were 414 HF patients who met our inclusion criteria including 287 (69.3%) HFpEF and 127 (30.6%) HFrEF cases. Comparative baseline characteristics both overall and stratified by type of HF and anemia status are shown in Table 1. Mean age was 62.65 ± 14.73 years and 55% of the population were women. The most common underlying diseases for HFpEF were hypertension (50.2%), diabetes (25.8%) and atrial fibrillation/flutter (24.4%), respectively. For HFrEF, these were hypertension 45 (35.4%), ischemic heart disease 41 (32.3%), diabetes 21 (16.5%), respectively.

Prevalence of anemia based on the WHO definition were 62.6%, 67.6% and 51.2% for the overall cohort, HFpEF and HFrEF groups, respectively. Mean Hb values of anemic male patients were 9.97 ± 1.95 g/dL for HFpEF and 11.02 ± 1.59 g/dL for HFrEF, respectively. Those values for anemic female patients were 9.57 ± 1.77 g/dL for HFpEF and 9.81 ± 1.42 g/dL for HFrEF, respectively. Overall, HF patients with anemia were significantly older (66 ± 14.72 vs 60 ± 13.65 years in HFpEF group, $p = 0.001$ and 62 ± 15.71 vs 56 ± 11.78 years in HFrEF group, $p = 0.012$). Anemia patients also had had higher prevalence of chronic kidney disease stage 3 or

Table 1
Baseline characteristics of the study population in total and stratified by heart failure type and anemia status.

Characteristic	Total (n = 414)	HFpEF (n = 287)			HFrEF (n = 127)		
		Anemia (n = 194)	Non-anemia (n = 93)	p value	Anemia (n = 65)	Non-anemia (n = 62)	p value
Female	228 (55%)	120 (62%)	51(55%)	0.257	33(51%)	24(39%)	0.172
Age (years)	62.65 ± 14.73	66 ± 14.72	60 ± 13.65	0.001	62 ± 15.71	56 ± 11.78	0.012
Hemoglobin (g/dL)							
Men	11.99 ± 2.52	9.97 ± 1.95	14.08 ± 0.87	<0.001	11.02 ± 1.59	14.45 ± 1.09	<0.001
Women	10.78 ± 2.25	9.57 ± 1.77	13.24 ± 1.17	<0.001	9.81 ± 1.42	12. 90 ± 0.92	<0.001
Hematocrit %							
Men	36.98 ± 8.23	30.98 ± 6.36	43.52 ± 6.91	<0.001	34.04 ± 4.32	43.94 ± 3.57	<0.001
Women	33.56 ± 6.60	30.06±0.5.21	40.52 ± 4.00	<0.001	30.90 ± 4.22	39.95 ± 3.14	<0.001
Creatinine (mg/dL)	1.90 ± 2.31	2.30 ± 2.90	1.22 ± 0.51	<0.001	2.20 ± 2.65	1.35 ± 0.46	0.014
GFR (mL/min/1.73 m^2)	48.20 ± 27.95	41.95 ± 25.13[a]	60.26 ± 29.16[b]	<0.001	41.68 ± 27.12[e]	55.72 ± 22.23[f]	0.003
SBP (mmHg)	134.54 ± 27.52	139.54 ± 28.26	133.42 ± 26.42	0.081	131.78 ± 27.98	123.52 ± 22.67	0.07
DBP (mmHg)	80.82 ± 17.97	77.94 ± 16.35	83.46 ± 19.21	0.012	82.23 ± 19.56	84.40 ± 17.99	0.519
Body mass index (kg/m^2)	23.99 ± 4.85	23.75 ± 3.58[c]	25.44 ± 5.57[d]	0.001	22.65 ± 5.47 [g]	23.64 ± 4.26 [h]	0.326
Ejection fraction (%)	52.99 ± 19.18	64.25 ± 11.75	62.23 ± 11.51	0.171	29.64 ± 6.81	28.36 ± 8.56	0.353
Charlson Comorbidity Index	1.85 ± 1.15	2.07 ± 1.30	1.44 ± 0.79	<0.001	2.03 ± 1.22	1.58 ± 0.74	0.014
Medical history							
Hypertension	189(46%)	106(55%)	38(41%)	0.029	27(42%)	18(29%)	0.141
Diabetes	95(23%)	60(31%)	14(15%)	0.004	11(17%)	10(16%)	0.904
Atrial fibrillation/flutter	85(21%)	42(22%)	28(30%)	0.118	10(15%)	5(8%)	0.201
Valvular heart disease	68(16%)	37(20%)	19(20%)	0.786	7(11%)	5(8%)	0.602
Ischemic heart disease	83(20%)	31(16%)	11(12%)	0.352	25(38%)	16(26%)	0.127
CKD (stage ≥ 3)	64(15%)	47(24%)	1(1%)	<0.001	14(22%)	2(3%)	0.002
History of stroke	21(5%)	10(5%)	5(5%)	0.937	5(8%)	1(2%)	0.106
Dyslipidemia	35(8%)	20(10%)	6(6%)	0.287	5(8%)	4(6%)	0.785
Current smoker	33(8%)	12(6%)	8(9%)	0.452	7(11%)	6(10%)	0.839
Current drinking	37(9%)	7(3%)	6(6%)	0.278	4(6%)	20(32%)	<0.01
Medication use							
ACEIs	70(17%)	34(16%)	13(13%)	0.447	15(23%)	8(13%)	0.137
ARBs	36(9%)	16(8%)	11(12%)	0.331	6(9%)	3(5%)	0.335
Beta-blockers	126(30%)	68(34%)	29(31%)	0.517	16(25%)	12(19%)	0.475
Diuretics	138(33%)	64(33%)	21(23%)	0.071	33(51%)	20(32%)	0.034
Spironolactone	18(4%)	7(3%)	4(4%)	0.775	4(6%)	3(5%)	0.745
Aspirin	132(32%)	62(32%)	17(18%)	0.018	31(48%)	22 (35%)	0.163
NSAIDs	19(5%)	8(4%)	8(9%)	0.112	3(5%)	–	0.087
PPIs	86(21%)	53(27%)	11(12%)	0.003	16(25%)	6(10%)	0.026

ACEIs = angiotensin converting enzyme inhibitors; ARBs = angiotensin receptor blockers; CKD = chronic kidney disease (stage ≥ 3), GFR = glomerular filtration rate; HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, NSAIDs = non-steroidal anti-inflammatory drugs; PPIs = proton pump inhibitors.
a = data missing for 25 HFpEF patients with anemia; b = data missing for 7 HFpEF patients with non-anemia; c = data missing for 54 HFpEF patients with anemia; d = data missing for 16 HFpEF patients with non-anemia; e = data missing for 6 HFrEF patients with anemia; f = data missing for 6 HFrEF patients with non-anemia; g = data missing for 15 HFrEF patients with anemia; h = data missing for 15 HFrEF patients with non-anemia.

Table 2
Clinical outcomes of the study population stratified by heart failure type and anemia status.

	HFpEF (n = 287)			HFrEF (n = 127)		
	Anemia (n = 194)	**No anemia (n = 93)**	**p value**	**Anemia (n = 65)**	**No anemia (n = 62)**	**p value**
Length of stay (days)	5.18 ± 3.46	4.7 ± 3.51	0.273	4.71 ± 4.00	3.82 ± 2.68	0.147
Rehospitalization	50 (26%)	24 (26%)	0.995	29 (45%)	23 (37%)	0.389
1-year all-cause mortality	39 (20%)	8 (9%)	0.014	13 (20%)	11 (18%)	0.569

HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

more (24% vs 1% in HFpEF group, p < 0.001 and 22% vs 3% in HFrEF group, p = 0.002). Other comorbidities such as hypertension and diabetes also tended to be more prevalent in the anemic group regardless of EF. The mean Charlson Comorbidity Index (CCI) indicated that anemic patients tended to have more comorbidity compared to non-anemic groups for both HFpEF (mean CCI: 2.07 ± 1.30 vs 1.44 ± 0.79; p < 0.001) and HFrEF (mean CCI: 2.03 ± 1.22 vs 1.58 ± 0.74, p = 0.014).

On admission, most commonly used medications were diuretics (33%), aspirin (32%), beta-blockers (30%), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) (26%), and spironolactone (4%). Length of stay was approximately 5 days. The rate of re-hospitalization was higher in HFrEF than HFpEF (40.94% vs 25.78%, p = 0.001). Overall, 1-year all-cause mortality of the cohort was 17.15%, which were 18.89% among HFrEF and 16.37% in HFpEF groups (Table 2).

When analyzed by anemic status, anemic patients had a significantly higher rate of mortality compared to the non-anemia group (20.08% vs 12.26%, p = 0.041) (Fig. 1). When stratified by severity of anemia, the mortality rates were 22.58%, 20.13% and 17.44% among those with Hb level of < 8.0 g/dL, 8.0–10.9 g/dL and 11.0–12.9 g/dL, respectively. After adjustment for confounding factors, anemia significantly and independently increased the 1-year all-cause mortality rate in HFpEF patients (20% vs 9%, HR = 2.667,

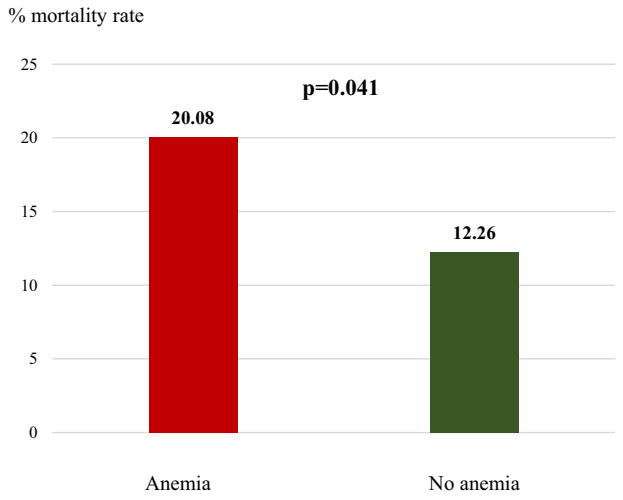

Fig. 1. The 1-year all-cause mortality by HF patients with/without anemia.

95% CI, 1.216–5.853, p = 0.014) but not in HFrEF patients (20% vs 18%, HR = 0.901, 95% CI, 0.376–2.155, p = 0.804). (Fig. 2 and Tables 3 and 4) In addition, untreated anemia was significantly associated with an increased mortality compared to those who received anemia treatment (adjusted HR 2.13, 95% CI, 1.13–3.99, p = 0.027) (Fig. 3).

4. Discussion

Among various comorbidities with adverse impact on HF progression, anemia may of one of the most common HF comorbidities in developing countries [16]. This may be a result of various reasons ranging from underlying health problems, lifestyles and poor diet. For Thailand, where there is an existing high rate of anemia among population, little is known about its impact on HF progression. As a result, we performed this study to add more information about relationship of anemia in Thai patients with HF.

Similar to previous studies, anemic patients tended to be older and with higher rates of comorbidities especially those that can lead to anemia such as chronic kidney disease [15,16,18]. Previous studies suggested that the effects of anemia on mortality disappeared after adjustment using a comprehensive comorbidity index such as the Charlson Comorbidity Index. We therefore calculated CCI for each individual patient and incorporated that in the regression model. After adjusting for covariates including CCI, results of our study clearly showed the independent and detrimental effects of anemia in patients with HF. There also appears to be a direct relationship between the severity of anemia and increasing rate of all-cause mortality in our study, similar to previous studies [15,19,20]. In addition, we also found that those who did not receive treatment for anemia had higher mortality compared to those who were treated. Taken together, these findings help reiterate the important influence of anemia on HF prognosis, especially in a population with high rate of anemia. While it is still debatable

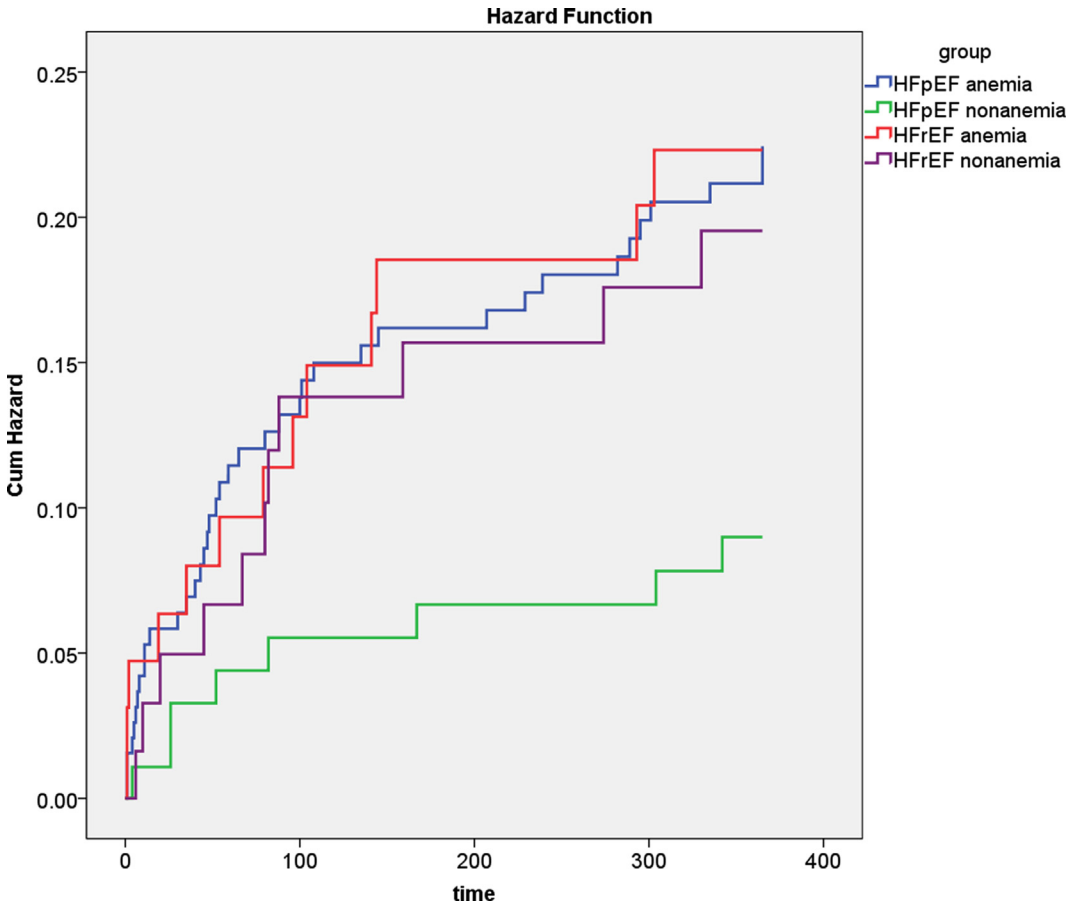

Fig. 2. Adjusted cumulative 1-year all-cause mortality stratified by HF type and anemia status. HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction. HFpEF; HR = 2.667 (1.216–5.853), Log rank p = 0.014. HFrEF; HR = 0.901 (0.376–2.155), Log rank p = 0.804. Adjustment factors: age, gender, smoking status, use of angiotensin converting enzymes or angiotensin receptor blockers, (ACEI/ARB), use of beta-blockers, hypertension and the Charlson Comorbidity Index (CCI).

Table 3
COX proportional regression analysis on the impact of anemia and other covariates on all-cause mortality in HFpEF patients.

Variables	Univariate Cox regression			Multivariate Cox regression		
	HR	95% CI	p value	HR	95% CI	p value
Anemia	2.500	1.168–5.349	0.018	2.667	1.216–5.853	0.014
Age	1.354	0.992–1.034	0.245	1.017	0.995–1.041	0.130
Gender	1.084	0.608–1.933	0.784	1.273	0.665–2.440	0.466
Smoker	0.638	0.252 – 1.612	0.342	0.678	0.247–1.859	0.450
Hypertension	1.712	0.951–3.083	0.073	1.881	0.953–3.713	0.069
Charlson Comorbidity Index	0.959	0.750–1.225	0.735	0.978	0.742–1.289	0.875
Use of ACEI/ARB	0.460	0.165 – 1.281	0.137	0.517	0.179–1.492	0.222
Use of beta-blockers	0.660	0.343–1.271	0.214	0.741	0.373–1.472	0.392

ACEI = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blockers.

Table 4
COX proportional regression analysis on the impact of anemia and other covariates on all-cause mortality in HFrEF patients.

Variables	Univariate Cox regression			Multivariate Cox regression		
	HR	95% CI	p value	HR	95% CI	p value
Anemia	0.870	0.390–1.942	0.734	0.901	0.376–2.155	0.804
Age	1.013	0.983–1.043	0.402	1.000	0.969–1.033	0.977
Gender	0.550	0.244–1.239	0.149	0.644	0.275–1.513	0.313
Smoker	2.882	0.389–21.346	0.300	1.855	0.230–14.940	0.562
Hypertension	0.528	0.237–1.175	0.117	0.598	0.244–1.464	0.260
Charlson Comorbidity Index	1.253	0.920–1.707	0.153	1.115	0.779–1.595	0.834
Use of ACEI/ARB	0.821	0.306–2.199	0.695	0.921	0.331–2.155	0.814
Use of beta-blockers	0.621	0.257–1.497	0.288	0.638	0.249–1.636	0.350

ACEI = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blockers.

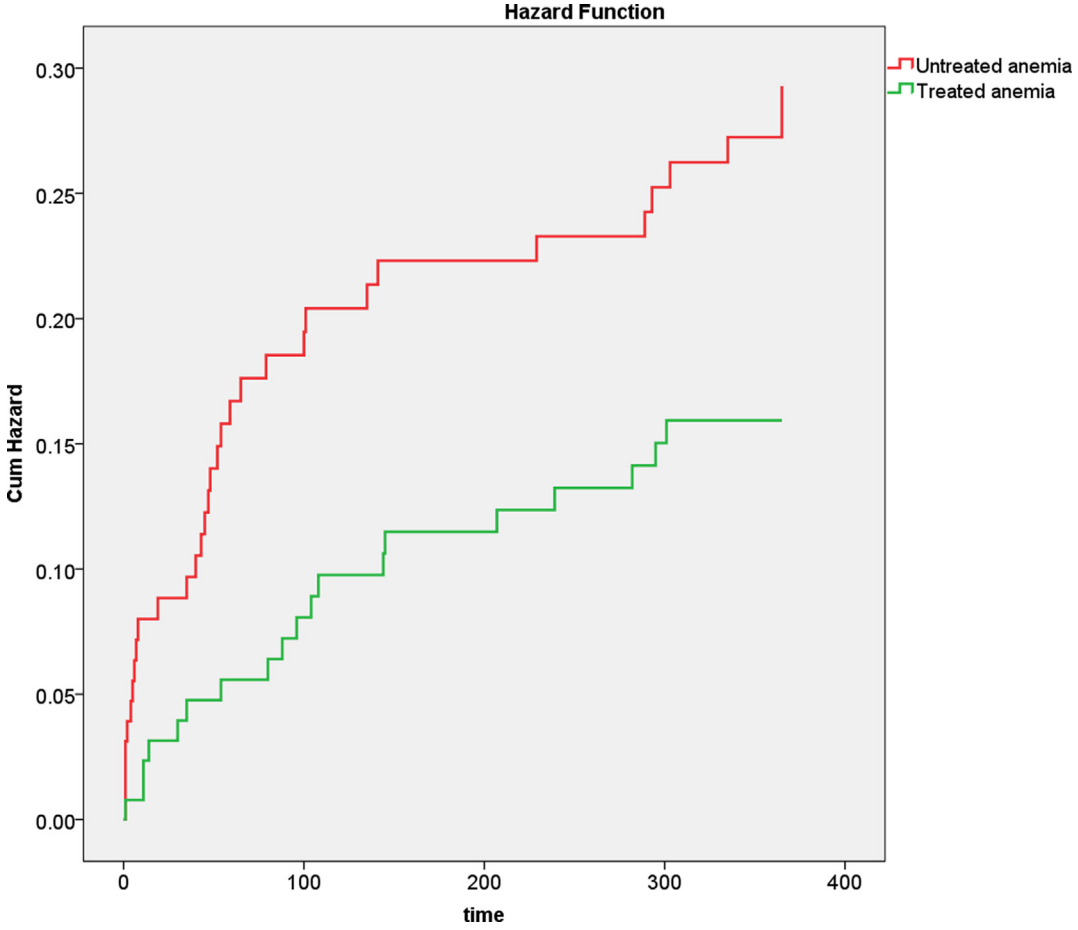

Fig. 3. Adjusted 1-year all-cause mortality of heart failure patients with anemia who received anemia treatment versus those without anemia treatment. Adjusted hazard ratio for all-cause mortality = 2.13 (95% CI: 1.130–3.999; p = 0.027) for heart failure patients with anemia who received anemia treatment versus those without anemia treatment. Adjustment factors: age, gender, smoking status, use of angiotensin converting enzymes or angiotensin receptor blockers, (ACEI/ARB), use of beta-blockers, hypertension and the Charlson Comorbidity Index (CCI).

whether anemia is merely a predictor of overall poor health or a disease that accelerate HF progression [19,21,22], we encourage healthcare professionals practicing in the developing countries to pay greater attention on the anemic status of HF patients and manage the patients accordingly. It is important to be reminded that the use of erythropoiesis-stimulating agents did not lead to HF improvement and increased rates of thromboembolic events and ischemic stroke in HF [22]. Since anemia is generally complex in nature, a thorough examination and treatment plan to address the correct underlying causes are crucial.

Nevertheless, we found only the impact of anemia on HFpEF but not with HFrEF. This may partly be from the fact that the 1-year all-cause mortality rate of HFrEF in our study was very high (18–20%) compared to studies conducted in developed Western countries (6.7–7.9%) [23]. In addition, the number of HFrEF in our study was relatively small (127 patients) and with low usage rate of recommended heart failure medication. As a result, the true impact of anemia on HFrEF in our study was masked by these issues.

Previous studies suggested that anemia adversely affect HF prognosis regardless of EF [15]. While most data came from HFrEF, data on the adverse impact of anemia in HFpEF patients have been conflicting [24–27]. This may partly due to the differences in patient population, study design, difference in the prevalence and severity of anemia in those studies. Larger studies tended to report a significant finding while smaller studies did not [24–27]. Nevertheless, anemia is undoubtedly a significant stress on the cardiovascular system. With decreased oxygen-carrying capacity, anemia has been shown to cause an increase in compensatory mechanisms such as sustained neurohormonal stimulation, mitochondrial dysfunction of myocardial cells, increased anaerobic metabolism and ultimately, cardiac remodeling [28–30]. Remodeling resulting from chronic compensatory mechanism induced by anemia can aggravate altered relaxation and increased stiffness of the ventricle commonly found in HFpEF [31,32]. However, current data is still limited and more studies are needed to clearly depict the relationship of anemia and HFpEF.

Another important issue to consider is the various potential causes of anemia [13]. Most if not all observational and epidemiological studies evaluating the impact of anemia on heart failure did not perform a rigorous evaluation on the causes of anemia [22]. Unfortunately, this study also had this same limitation. However, a recent meta-analysis of 41 studies in 3,317 heart failure patients suggested that impaired erythropoietin production is the major cause of anemia in heart failure patients [33]. In addition, severity of anemia was found to be increased with increasing age and disease severity. Based on this fact along with previous local studies, anemia from chronic kidney disease and iron deficiency anemia are the most likely causes of anemia in our population [33,34].

The usage rates of guideline directed medical therapy (GDMT) among HFrEF were low in our study with 25%, 22% and 6% usage of ACEIs/ARBs, beta-blockers, and spironolactone, respectively. These data clearly shown underutilization of neurohormonal blockers proven to reduce morbidity and mortality. This may explain very high mortality rate in our population. Shortage of cardiologists during the study period, substandard health literacy and access to care may partly explain such underutilization of GDMT.

Our study had several limitations. First, data were obtained from a single hospital. As a result, a large, multicenter study should be further conducted to confirm our findings. Second, our study population had a larger ratio of HFpEF than HFrEF. A previous study conducted in Thailand in 2010 reported that around 60% of Thai heart failure patients had HFpEF. This rate is even higher in our study. Although we do not know with certainty the true reason for this finding, untreated and poorly controlled hypertension, a well-known cause for HFpEF in this rural area may be a potential reason for this finding. Third, we had to exclude about 50% of the patients admitted with HF in the study site due to the referral system of the country where patients were referred back to primary and secondary hospitals for long term follow-up. This exclusion may also had an impact on the ratio of HFpEF versus HFrEF in our study. Fourth, we were unable to perform a thorough analysis on the causes of anemia due to the limitation of incomplete work-up of related laboratory tests. Fifth, we did not conduct analysis on the impact of changes in Hb level versus outcome with time. Lastly, due to the inherited characteristics of observational study, our results were susceptible to the influence of confounding factors despite our best efforts to perform statistical adjustment. Based on these limitations, we were unable to draw a firm conclusion that anemia is the direct cause of increased mortality in our study population. Despite these limitations, to our knowledge, this is the first study that evaluate the impact of anemia on HF prognosis conducted in a developing country. Findings from our study should help raise awareness on the importance of anemia in HF patients in countries with similar healthcare context.

5. Conclusion

Among Thai HF patients, anemia was very common afflicting more than 60% of HF patients. Anemic patients tended to be older and with higher rates of comorbidities. Anemia was independently associated with a significant increase in all-cause mortality in HF patients. The risk also increased with increasing severity of anemia. Based on these findings, healthcare professionals practicing in developing countries should be aware of the importance of anemia on HF prognosis. Attempts to detect, evaluate and manage anemia in HF patients should be incorporated in HF care plan, particularly among developing countries.

Statement of authorship:

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100597.

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