Patients with HFpEF and HFrEF have different clinical characteristics but similar prognosis: a retrospective cohort study

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Abstract

Background: Globally, heart failure (HF) has been recognized as one of the major cardiovascular disorder with high morbidity, mortality and considerable social impact. In Sub Saharan African countries, HF has turned out as a leading form of cardiovascular diseases, and has considerable socioeconomic impact. However, there are differences in clinical characteristics and survival status among patients with preserved (HFpEF) and reduced (HFrEF) ejection fraction. The aim of this study is to outline the clinical characteristics and medication profile, assess the survival status and prognostic factors of Ethiopian HF patients with HFrEF and HFpEF.

Methods: A retrospective cohort study was carried out and we employed medical records of patient's, admitted as a result of HF to the University of Gondar Referral Hospital in the period between December 02, 2010 and December 01, 2015 due to HF. Kaplan Meier curve was used to analyze the survival status and log rank test was used to compare the curves. Cox regression was used to analyze independent predictors of mortality in all HF patients.

Results: Of the 850 patients who were admitted due to HF, 311 patients met the inclusion criteria. Majority of the patients had HFpEF (52.73%) and tend to be women (76.22%). They predominantly had etiologies of valvular and hypertensive heart diseases, and took calcium channel blockers and anticoagulants. Conversely, patients with HFrEF had etiologies of ischemic heart disease and dilated cardiomyopathy and were prescribed angiotensine converting inhibitors (ACEI) and beta blockers. Kaplan Meier curves and Log rank test ($p = 0.807$) showed that there was no statistically significant difference in the mortality difference among patients with HFpEF and HFrEF. On the other hand, Cox regression analysis showed advanced age, lower sodium level, higher creatinine level and absence of medications like ACEI, spironolactone and statins independently predicted mortality in all HF patients.

Conclusions: Different clinical characteristics were found in both groups of HF patients. There was no difference in survival outcome between patients with HFrEF and HFpEF.

Keywords: Heart failure, Ejection fraction, Clinical characteristics, Survival, Ethiopia

Background

Heart failure (HF) is one of the major cardiovascular disorder with high morbidity and mortality and rising costs, which account for 1–2% of the annual health budget of most developed nations [1, 2]. HF primarily involves (affects) people with advanced age, and incidence and prevalence increases progressively in those age > 60 years [3]. The most frequent prevalence estimate for the adult population at large is 2% and more than 10% particularly in those aged 75 years and older [2, 4–6]. In Sub Saharan African countries (SSA), HF has turned out as a leading form of cardiovascular disease, and has considerable socioeconomic impact owing to its high prevalence, mortality and impact on young generations [7]. Unlike developed nations, the most prevailing causes of HF in Africans remains largely non ischemic [7]. Two third of HF cases in SSA are mainly secondary to Hypertension (HTN), cardiomyopathy and rheumatic heart disease [7, 8]. In contrast, in industrialized nations, coronary
artery disease, either alone or in combination with HTN, is the prominent cause of HF [9, 10].

Left ventricular dysfunction (LVD) is categorized into systolic and diastolic dysfunction. A LVEF above 50% and below 40 are considered reserved and reduced ejection fractions, respectively, leaving an intermediary range of 40 to 50% [11]. Irregularity in the filling properties or capacity of the left ventricle in patients with LVEF > 50 is used to classify diastolic dysfunction [11, 12]. HF is usually considered typical when presenting in patients with dilated hearts and systolic dysfunction (ejection fraction (EF)<40%). As a result, the most therapeutic evidence, including effective pharmacological and device therapies that have led to impressive improvements in survival is in this group of patients with HFrEF. By contrast, most clinical trials excluded patients with HFrEF. Therefore, there are disparities on the prognosis of patients with SDf and DDf as some researches demonstrated that morbidity and mortality is worse in the earlier group while other studies emphasize that there is no convincing discrepancy in prognosis between these groups [13, 19–22].

The etiology of HF was determined based on the following algorithm: Ischemic, when the patient was diagnosed with ischemic heart disease (IHD); Valvular, when there was moderate valulopathy with no IHD; Hypertensive, when there was previous history of hypertension but no evidence of additional cardiovascular disease; Dilated cardiomyopathy (DCMP), when there was no other known cardiac cause and had LVEF < 50%; and Cor pulmonale, when right sided heart failure without left ventricular dysfunction is present.

Statistics
Statistical analysis was conducted for both quantitative and qualitative variables. Group variables were indicated in percentage and Chi square test was used. A probability of type I error <5% was considered significant. Continuous variables were revealed in mean ± SD and independent t – test was used with a probability of type I error < 5% considered significant. Kaplan – Meier survival curves were designed and analyzed with the Mantel log rank test to measure the significance. Univariate Cox regression analysis was used to determine the co-factors with momentous outcome on all-cause mortality. Multivariate Cox regression analysis was implemented to determine the independent foreshadowing factors for all-cause death. All data were analyzed with SPSS version 20.0 (SPSS Inc. Chicago, IL) software for windows.

Results
Of 850 patients who were admitted to GURH due to HF, in the period between December 02, 2010 and December
01, 2015, 311 patients met the inclusion criteria. From the study group, 164 patients had HFpEF (EF ≥ 50%) and the remaining participants (147) had HFrEF (EF < 50%). Table 1 shows baseline clinical characteristics of the two groups. The mean age of the participants were 53.58 (±16.902) years with no significant divergence among the groups (54.20 (±16.587) Vs.52.88 (±17.246), \( P = 0.496 \)), and women accounted for the majority of patients with LVEF ≥ 50 (76.22% vs. 62.59%, \( P = 0.009 \)). Analysis of cardiovascular risk factors such as hypertension and diabetes, other co morbidities like anemia, atrial fibrillation, and NYHA functional class revealed no compelling variance among the groups. However, heart failure etiology clearly distinguished between the HFrEF and HFpEF groups. In the earlier groups Ischemic heart disease (IHD) (21.09% vs. 10.98%, \( P = 0.015 \)) and DCMP (21.77% vs. 4.27%, \( P < 0.001 \)) were more prevalent; whereas, VHD (34.01% vs. 45.96%, \( P = 0.020 \)) and HHD (11.56% vs. 20.12%, \( P = 0.040 \)) were more prevalent in the later groups. There were also significant differences between patients with HFpEF and HFrEF in their heart rate (95.60 (±21.177) Vs.89.93 (±16.287), \( P = 0.009 \)).

**Medical treatment**

Table 2 compares treatments at discharge in patients in the two groups. There were no significant difference in the prescription of diuretics, spironolactone, antiplatelet agents, digoxin and statins. Patients classified as having depressed LVEF were usually prescribed angiotensin converting enzyme inhibitor (ACEI) and beta blockers. On the other hand, anti-coagulants and calcium channel blockers were more frequently prescribed in patients with HFpEF.

**Results of laboratory analyses and echocardiograms**

Higher hemoglobin levels were measured in patients with reduced ejection fraction than preserved ejection fraction (13.31 ± 3.76 vs. 12.47 ± 3.08, \( P = 0.031 \)). Greater ventricular dimension were recorded in patients with HFrEF (57.38 ± 9.07 vs. 46.10 ± 8.64, \( P < 0.001 \)). The mean EF in patients with preserved and reduced EF were 62.57 ± 8.62 and 40.36 ± 6.81 respectively (Table 3).

**Survival analysis**

The mean duration of follow up was 24.56 ± 17.79 months. Mortality were 14.02% in patients with HFpEF (23 patients) and 14.29% in patients with HFrEF (21 patients). Kaplan Meier survival curves (Fig. 1) shows there were no significant difference in survival status of patients with HFrEF and HFpEF (Log Rank test, \( P = 0.807 \)). On the other hand, univariate Cox regression analysis showed that age, sodium level, creatinine level, IHD, Spironolactone, and digoxin were significantly associated with mortality in patients with HF (Table 4). Multivariate Cox regression analysis, including the significant predictors of mortality

### Table 1 Clinical characteristics of Heart Failure patients based on Preserved of reduced ejection fraction

| Variable          | Total patients (\( n = 311 \)) | LVEF ≥ 50% (\( n = 164 \)) | LVEF < 50% (\( n = 147 \)) | \( P \) value |
|-------------------|---------------------------------|-----------------------------|----------------------------|--------------|
| Women, n (%)      | 217 (69.77)                     | 125 (76.22)                 | 92 (62.59)                 | 0.009        |
| Age, Years (mean ± SD) | 53.58 ±16.902                  | 54.20 ±16.587              | 52.88 ±17.246              | 0.496        |
| Anemia, n (%)     | 118 (37.94)                     | 65 (39.63)                  | 53 (36.05)                 | 0.516        |
| AF, n (%)         | 79 (25.41)                      | 47 (28.66)                  | 32 (21.77)                 | 0.163        |
| DM, n (%)         | 4 (1.29)                        | 2 (1.22)                    | 2 (1.36)                   | 0.912        |
| Hypertension, n (%) | 97 (0.312)                     | 56 (34.15)                  | 41 (27.89)                 | 0.235        |
| Heart Rate ( mean ± SD) | 92.88 ±19.166             | 95.60 ±21.177              | 89.93 ±16.287              | 0.009        |
| Systolic BP       | 122.75 (±24.231)                | 125.06 (±26.911)            | 120.18 (±20.651)           | 0.072        |
| NYHA Functional Class | 82 (26.37)                  | 39 (23.78)                  | 43 (29.25)                 | 0.274        |
| Class III, n (%)  | 229 (73.63)                     | 125 (76.22)                 | 104 (70.75)                |              |
| Etiology          |                                 |                             |                            |              |
| IHD, n (%)        | 49 (15.76)                      | 18 (10.98)                  | 31 (21.09)                 | 0.015        |
| HHD, n (%)        | 50 (16.08)                      | 33 (20.12)                  | 17 (11.56)                 | 0.040        |
| VHD, n (%)        | 127 (40.84)                     | 77 (46.95)                  | 50 (34.01)                 | 0.020        |
| DCMP, n (%)       | 39 (12.54)                      | 7 (4.27)                    | 32 (21.77)                 | <0.001       |
| Cor pulmonale, n (%) | 14 (4.50)                      | 9 (5.48)                    | 5 (3.40)                   | 0.376        |
| Others, n (%)     | 32 (10.29)                      | 20 (12.20)                  | 12 (8.16)                  | 0.243        |

AF atrial fibrillation, BP blood pressure, DCMP dilated cardiomyopathy DM diabetes mellitus, HHD hypertensive heart disease, IHD ischemic heart disease, NYHA New York Heart Association, SD standard deviation
identified on univariate Cox regression, showed that advanced age, low sodium level, high creatinine level, and absences of medications (spironolactone, ACEI and satin) significantly predicted morality (Table 4).

**Discussion**

The present research analyzed data from a retrospective observational cohort of HF patients to assess clinical characteristics, medication profile and determinants of mortality among HF patients with HFrEF and HFpEF who were admitted at GURH.

The prevalence of HFpEF is on the rise with period in developed nations [13, 23], varies depending on the age of the patient, race and the cutoff values for LVEF. In spite of that, there is a pervasive agreement that HFpEF is prominent in more than a third of all patients admitted with HF [19, 24–27]. In our study, the prevalence of HFpEF was 52.73% which was in alignment with other studies [28–30]. A recent study conducted by L. Martínez-Braña et al. found that prevalence of HFpEF in Spain was 72.2% [20]. A study carried out in Japan by H. Kaneko et al. reported that prevalence of HFpEF was 72% [31]. In the Identification of Patients With Heart Failure and PREserved Systolic Function (I PREFER) prevalence of HFpEF was about 65% [32]. The disparity between these findings and our study might be credited to sample size variation of the study population, age of the patients, race and cutoff values for LVEF during the study.

Patients with HFP EF are at advanced age, women and more often have hypertension compared to patients with HFrEF [20, 25, 27, 31]. In a systematic review reported by E. E.S. van Riet et al., HFP EF was more prevalent with age > 60 years and female gender [1]. In a meta-analysis study, compared with patients with HFrEF, those with HFP EF were older and more often women, and have a history of hypertension [10]. The differences in patients’ backgrounds in our study were almost indistinguishable to those of previous articles as patients with HFpEF in this study were older and more often female.

Regarding the etiology of HF, hypertensive heart disease (HHD) and VHD are more common in patients with HFP EF. Whereas, in patients with HFrEF, the most prevalent causes were IHD and DCMP [19, 20, 24, 26]. A meta-analysis conducted by R.N. Doughty et al reported that, compared with the HFrEF patients, those with HFP EF more often had a history of Hypertension and less likely had IHD [10]. In I PREFER, Irbesartan clinical trial and the Effects of Candesartan for the Management of Patients With Chronic Heart Failure (CHARM) program, it were reported that HHD was the most important etiologic factor for the diagnosis of HFpEF and CAD is the leading cause for patients with HFrEF [32–34]. Similar finding were documented in our study, where IHD and DCMP were the leading etiologies for the prevalence of HFrEF; in contrast, VHD and HHD were responsible for the diagnosis of HFpEF. One of the interesting finding in our study was, the impact of IHD as an etiology of HF in patients with reduced ejection fraction. According to prior literatures, most of the etiologies in African population were non ischemic [7]. This disparity might indicate that the progressive change in the epidemiological pattern of the disease through time and the modification of individuals’ life style.

In terms of drug treatment, ACEI, Beta – Blockers and Digitalis are mostly prescribed to patients with HFrEF [19, 26, 31, 35–37]. However, CCB are usually indicated for patients with HFP EF [38]. This is further supported.

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**Table 2** Medication profile of heart failure patients based on ejection fraction

| Medication       | LVEF ≥ 50 (n,164) | LVEF < 50% (n,147) | P value |
|------------------|-------------------|-------------------|---------|
| ACEI n, %        | 34 (15.85)        | 80 (40.82)        | <0.001  |
| Beta Blocker n, %| 45 (21.95)        | 73 (36.73)        | <0.001  |
| Diuretics n, %   | 146 (74.39)       | 136 (70.75)       | 0.290   |
| Spironolactone n, %  | 114 (57.93) | 95 (48.99) | 0.359   |
| Digoxin n, %     | 46 (23.17)        | 33 (17.69)        | 0.257   |
| Statin n, %      | 24 (11.59)        | 30 (13.61)        | 0.180   |
| Anticoagulants n, % | 33 (17.07) | 12 (14.70) | 0.003   |
| Antiplatelet agents n, % | 33 (15.24) | 39 (17.69) | 0.181   |
| CCB n, %         | 21 (9.76)         | 7 (4.76)          | 0.013   |

ACEI angiotensin converting enzyme inhibitor, CCB calcium channel blocker

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**Table 3** Laboratory and echocardiography results of heart failure patients based on ejection fraction

| Variable          | LVEF ≥ 50 (n,164) | LVEF < 50% (n,147) | P value |
|-------------------|-------------------|-------------------|---------|
| Hgb (Mean ± SD)   | 12.47 ± 3.08      | 13.31 ± 3.76      | 0.031   |
| Cr (Mean ± SD)    | 1.1086 ± 0.774    | 1.0690 ± 0.536    | 0.598   |
| Sodium (Mean ± SD)| 134.86 ± 5.44     | 135.31 ± 7.92     | 0.563   |
| LVEDD in mm (Mean ± SD) | 46.10 ± 8.64 | 57.38 ± 9.07 | <0.001 |
| LVEF% (Mean ± SD) | 62.57 ± 8.62      | 40.36 ± 6.81      | <0.001  |

Hgb hemoglobin, Cr creatinine, LVEDD left ventricular end diastolic diameter, LVEF left ventricular ejection fraction, SD standard deviation
**Log rank test, P = 0.807**

**Fig. 1** Kaplan Meier survival curves at 60 months for patients with preserved and reduced ejection fraction

**Table 4** Predictors of mortality to all causes of heart failure

| Variables          | Univariate analysis | Multivariate analysis |
|--------------------|---------------------|-----------------------|
|                    | Hazard ratio (95% CI) | Hazard ratio (95% CI) | P value |
| Gender             | Male                | 0.984 (0.521–1.857)   | 1.132 (0.463–2.766) | 0.785 |
| Age, Years         | Age, years          | 1.046 (1.025–1.068)   | 1.045 (1.016–1.076) | 0.002 |
| NYHA Class         | Class IV            | 1.549 (0.719–3.337)   | 1.267 (0.527–3.046) | 0.597 |
| Anemia             | Yes                 | 1.483 (0.818–2.689)   | 0.708 (0.333–1.504) | 0.369 |
| Sodium, mEq/L      |                     | 0.933 (0.896–0.972)   | 0.913 (0.851–0.980) | 0.011 |
| Creatinine, mg/dl  |                     | 2.602 (2.052–3.300)   | 1.966 (1.369–2.824) | <0.001 |
| AF                 | Yes                 | 0.486 (0.225–1.051)   | 0.617 (0.171–2.224) | 0.461 |
| VHD                | Yes                 | 0.636 (0.342–1.185)   | 1.420 (0.413–4.886) | 0.578 |
| IHD                | Yes                 | 2.355 (1.882–4.691)   | 2.211 (0.397–12.331) | 0.365 |
| DCMP               | Yes                 | 0.898 (0.352–2.290)   | 1.068 (0.240–4.743) | 0.931 |
| HHD                | Yes                 | 1.036 (0.481–2.229)   | 1.272 (0.338–4.794) | 0.722 |
| LVEF               |                     | 0.997 (0.975–1.020)   | 0.992 (0.958–1.027) | 0.634 |
| Diuretics          | Yes                 | 0.877 (0.269–2.858)   | 0.690 (0.180–2.650) | 0.589 |
| Spironolactone     | Yes                 | 0.388 (0.214–0.703)   | 0.343 (0.158–0.743) | 0.007 |
| ACEI               | Yes                 | 0.952 (0.510–1.778)   | 0.258 (0.098–0.680) | 0.006 |
| Beta Blocker       | Yes                 | 1.205 (0.659–2.204)   | 1.713 (0.766–3.832) | 0.190 |
| Digoxin            | Yes                 | 0.313 (0.132–0.746)   | 0.407 (0.095–1.736) | 0.224 |
| Antiplatelet       | Yes                 | 0.883 (0.435–1.793)   | 1.383 (0.352–5.436) | 0.643 |
| Anticoagulants     | Yes                 | 1.700 (0.817–3.541)   | 2.429 (0.845–6.978) | 0.099 |
| Statin             | Yes                 | 1.520 (0.768–3.010)   | 0.189 (0.037–0.972) | 0.046 |
| CCB                | Yes                 | 1.555 (0.720–3.359)   | 0.815 (0.287–2.317) | 0.701 |

ACEI angiotensin converting enzyme inhibitor, AF atrial fibrillation, CCB calcium channel blocker, DCMP dilated cardiomyopathy, HHD hypertensive heart disease, IHD ischemic heart disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, VHD valvular heart disease

Factors included in multivariate Cox model include: Gender, Age, NYHA Class, presence of comorbidities such as anemia and AF, Common etiologies of HF such as VHD, IHD, HHD, and DCMP, Use of medications such as Diuretics, Spironolactone, ACEI, Beta Blocker, Digoxin, Antiplatelet, Anticoagulant, Statin and CCB, and laboratory values such as sodium and creatinine.
by 2016 ESC European heart failure guideline, as indicated amiodipine in HF patients with preserved ejection fraction and ventricular rhythm problem [39]. Unlike HF with HFrEF, patients with HfPEF did not benefit from the novel medications indicated to manage the disease and improve morbidity and mortality. Hence, there are few clinical trials on this group of patients and trials already conducted on ACEI/Angiotensin Receptor Blockers showed that there is no promising influence on reducing the mortality rate in patients with HfPEF [33, 40]. The CHARM Program study showed no significant effect on mortality, but showed significant benefit in preventing HF hospitalization [34]. One of the proposed predictions by Y. Juillièrre et al. was systemic hypertension is more frequently associated with preserved ejection fraction, resulting a higher rate of prescription of CCB. In contrast most of the etiologies in patients with HFrEF are usually IHD [38]. Similar findings were presented in our study, where most of patients with HfPEF took CCB and anticoagulants since hypertension and AF were more prevalent in this group of patients. However, ACEI and Beta blockers were more recommended in patients with HFrEF.

There is no clear cut variation in the long term clinical outcomes of patients with HfPEF and HFrEF. Studies conducted by Owan TE et al., F.P. Brouwers et al. and H. Kaneko et al. reported that patient with HfPEF had better prognosis than those with HFrEF [13, 31, 41]. Nonetheless, no significant variation in mortality between patients with preserved and reduced LVEF were reported by other studies [19, 20, 26]. In the current study, there was no substantial difference (Log rank test, $P = 0.807$) in the survival status of patients with preserved and reduced ejection fraction. However, patients with HfPEF had a relatively better survival status.

In the current study, multivariate cox regression analysis exhibited that the independent prognosticators of all causes of death in patients with HF were advanced age, low sodium level, high creatinine level, and absence of medications like statins, ACEI, and Spironolactone. Our findings were consistent with various studies; in a prospective study conducted by Macín SM, et al. [19] and Ojeda S, et al. [26] in Spain and a retrospective study in USA by Owan TE et al. [13] reported that advanced age, lower level of sodium, higher serum creatinine level as a predictor of unfavorable outcome in HF patients. In a retrospective study done by H. Kaneko et al. [31] found that absence of statins in patients with HFrEF medication prescription as a prognosticator of mortality. In a randomized control trial conducted by Pitt B et al. [42], it was reported that aldosterone blockers had a momentous importance in lowering morbidity and mortality by decreasing atrial natriuretic peptide concentrations. The study of left ventricular dysfunction (SOLVD) determined that addition of ACEI in HF treatment had significantly decreased mortality and morbidity in patients with HFrEF [43].

**Study limitation**

Our study had several limitations. First, this study was carried out in a single center so the outcomes of the research cannot be generalized to all medical centers. Second, the sample size of the study population may not be sufficient enough to detect statistically significant differences. Third, the definition of HFrEF and HfPEF in the current study was based on LVEF, and it therefore remains not certain whether the study participants had objective documentation of diastolic dysfunction, as characterized by guiding principle for the diagnosis of HfPEF.

Despite these limitations, we believe that our study provides vital information on the clinical features and prognosis of patients with HF. Moreover, it will give a blue print for further clinical research in the area.

**Conclusions**

In the current study, majority of the patients presented with HFpEF. As in other studies, women, hypertensive and VHD etiologies were more predominant in patients with HFpEF and takes CCB and anticoagulants. Patients with HFrEF had IHD and DCMP etiologies. They usually took Beta blockers and ACEI. There was no compelling disparity in mortality between patients with HFrEF and HFpEF. However, older age, lower sodium level, higher creatinine level and absence of medications like ACEI, spironolactone and statins independently predicted mortality in all HF patients. These outcomes indicated that further research should be conducted and several factors should be considered for preserved or reduced LVEF management.

**Abbreviations**

ACEI: Angiotensin-converting enzyme inhibitor; AF: Atrial fibrillation; CAD: Coronary artery disease; CCB: Calcium Channel Blockers; CHARM: The Effects of Candesartan for the Management of Patients With Chronic Heart Failure; Cr: Creatinine; DCMP: Dilated cardiomyopathy; DDF: Diastolic dysfunction; DM: Diabetes mellitus; EF: Ejection fraction; GURH: Gondar University Referral Hospital; HF: Heart failure; HfPEF: Heart Failure with preserved Ejection Fraction; HFrEF: Heart Failure with reduced Ejection Fraction; Hgb: Hemoglobin; HHD: Hypertensive heart disease; HTN: Hypertension; I PREFER: Identification of Patients With Heart Failure and Preerved Systolic Function: an epidemiological regional study; IHD: Ischemic heart disease; LVEDD: Left ventricular end diastolic dimension; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; SD: Standard deviation; SDF: Systolic dysfunction; SOLVED: The study of left ventricular dysfunction; SSA: Sub Saharan Africa; VHD: Valvular heart disease

**Acknowledgement**

We would like to acknowledge staffs from medical records departments for organizing and searching patient’s medical charts.

**Funding**

No funding source.
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Consent for publication
Not applicable.

Ethics approval and consent to participate
Ethical clearance was obtained to access patients medical records from GURH ethical board of School of Pharmacy. Since the data collection was conducted retrospectively from patient medical records, and patients were not directly involved in data collection, informed consent was not sought from patients.

Received: 29 July 2016 Accepted: 16 November 2016

Published online: 21 November 2016
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