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The usefulness of Charlson Comorbidity Index (CCI) scoring in predicting all-cause mortality in Outpatients with Clinical Diagnoses of COPD

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Abstract

Background: Since comorbid conditions are frequently present in chronic obstructive pulmonary disease (COPD) and affect outcome, a composite scoring system to quantify comorbidity might be helpful in assessing mortality risk.

Methods: We tested the hypothesis that the Charlson Comorbidity Index (CCI) score at the time of an outpatient medical clinic encounter for COPD predicts all-cause mortality. Cox Proportional Hazards analyses were used in 200 randomly selected patients to relate CCI scores to all-cause mortality out to 5 years.

Results: Mean age was 62 ± 10 years, 56% were female, FEV1 was 62%, CCI was 3.08 ± 2.30, and 30% had a CCI ≥ 4, indicating 3 or more comorbid conditions. All-cause mortality was 8.5% and 20% at 3 and 5 years, respectively. In univariate testing, the CCI score and hospitalizations predicted mortality, but FEV1 did not. In multivariable testing, which included covariates of age, sex, socioeconomic status, race, FEV1 percent-predicted, and all-cause hospitalizations in the preceding year, CCI expressed as a continuous variable strongly predicted mortality: hazard ratio (HR) 1.38 for each unit increase in the score ($p < 0.0001$). While 1 or 2 comorbid conditions were not significantly related to mortality, 3 or more comorbid conditions (compared to none) strongly predicted mortality: HR 9.80, 95% CI 3.80 to 25.00.

Conclusion: Comorbidity, assessed with the CCI, is strongly predictive of mortality in outpatients with a clinical diagnosis of COPD, and this relationship appears to be non-linear. This instrument may be useful in determining prognosis in this population.

Keywords

COPD, Comorbidity, charlson comorbidity index, CCI, mortality

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Introduction

In 2020, chronic obstructive pulmonary disease (COPD) was listed by the Centers for Disease Control (CDC) as the sixth leading cause of death in the United States, falling behind heart disease, cancer, COVID-19, accidents, and stroke.[1] Globally, COPD has risen to the third leading cause of death.[2] However, individuals with COPD often die with this disease rather than from this disease, since frequently

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occurring[3] and often severe comorbid conditions strongly influence prognosis in this disease.[4] Comorbidity can be defined as "*any distinct additional entity that has existed or may occur during the clinical course of a patient who has the index disease under study*".[5,6] Others have suggested that mere co-occurrence of a condition (such as color blindness) is not sufficient to define comorbidity; rather the condition must affect diagnosis, treatment or prognosis in the individual with the primary illness.[7]

In general, there is an inverse relationship between the severity of airflow limitation in COPD (using FEV1 as its marker) and the likelihood of coexisting conditions being the primary cause of death. For individuals with severe airflow limitation, COPD is the more likely cause of death. However, for those with mild airflow limitation, lung cancer and cardiovascular disease are more likely causes of mortality.[8] Other markers of COPD severity, including the use of supplemental oxygen therapy, a history of hospitalization for COPD, and hospital readmission after an exacerbation increase the burden of this disease and also contribute to mortality risk.[4]

Since comorbidity is common in COPD and often contributes to mortality risk, we explored its prognostic importance in patients with this disease. To this end, we assessed comorbidity in a random sample of COPD outpatients in a medical clinic setting using the Charlson Comorbidity Index (CCI), and tested this as a predictor of all-cause mortality.

Methods

We tested the hypothesis that higher levels of comorbidity, as measured by the CCI at the time of an index outpatient medical clinic encounter predicts subsequent all-cause mortality in COPD outpatients - even after controlling for some aspects of primary disease severity and selected demographic characteristics.

Following IRB approval, we reviewed a randomly chosen convenience sample of 200 electronic records of patients enrolled at the outpatient medical or pulmonary clinics of one urban tertiary care hospital who had at least one medical or pulmonary clinic encounter between January 1, 2015, and December 31, 2019. This record review was performed by one investigator assigned solely to this task. For randomization, unique, randomly generated numbers were assigned to each patient, then we reviewed consecutively increasing numbered records until an n of 200 eligible records was reached.

Selection criteria required all of the following: 1) Age range 40 to 89 years; 2) A principal diagnosis of COPD at the time of the index clinic visit, based on the following ICD-10 codes: J41.8 - mixed simple and mucopurulent chronic bronchitis; J42 - unspecified chronic bronchitis; J43.1 – panlobular emphysema; J43.2 - centrilobular emphysema; J43.8 - other emphysema; J43.9 - emphysema, unspecified; J44.0 - chronic obstructed pulmonary disease with (acute) lower respiratory infection; J44.9 - chronic obstructed pulmonary disease, unspecified; and 3) Record documentation of at least one spirometry measurement. Airflow limitation in those meeting spirometric confirmation of COPD (FEV1/FVC < 0.70) into mild, moderate, severe and very severe was made using Global Initiative for Obstructive Lung Disease (GOLD) criteria.[9]

The first reviewed clinic COPD encounter (either the first or follow-up) over the above time range was considered the index visit, representing time zero for the survival analysis. A look-back manual record review of patient information from the index medical clinic encounter and discharge data (if available) were used to obtain patient demographics, severity data, and the presence of comorbid conditions. Comorbid conditions were included only if they were present at the time of the index visit. Medical record documentation and the State of Connecticut Department of Public Health vital statistics database information were used to determine mortality and – if documented - date of death. Matching of medical record information and vital statistics documentation was made using patient name, date of birth, and address. If no match was obtained, the patient was considered alive.

The dependent variable was all-cause mortality out to 5 years from the index visit. Independent (predictor) variables included: 1) a Chart Review Version of the Charlson Comorbidity Index (CCI) score, entered into the model as either a continuous variable or a categorical variable; 2) patient demographics: age, sex, race; 3) and two COPD disease severity markers, FEV1 percent-predicted and the number of all cause hospitalizations occurring in the 12 months before the index encounter. We chose all-cause rather than respiratory-caused hospitalizations since, as is the case for determining the cause of mortality,[10] adjudication of causal factors in complex COPD patients is often problematic. Smoking history information and supplemental oxygen use were not abstracted.

For the CCI,[11,12] each of the following conditions was given a score of 1: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, and diabetes with no complications. Each of the following conditions was given a score of 2: hemiplegia or paraplegia, renal disease, and tumors including leukemia, and lymphoma. Moderate to severe liver disease was each given a score of 3, while metastatic tumors or acquired immunodeficiency syndrome (AIDS) were each given a score of 6. The sum of the above weights were added to give a numerical CCI score, which was used in the analysis. Of note, since the primary disease in our patients, COPD, is included among the comorbid conditions (chronic respiratory disease)

comprising the instrument, a score of 1 in our study indicates COPD without CCI comorbidity.

Descriptive data are expressed as means ± standard deviations (SD) for variables with normal distribution, as median and IQR for those without non-normal distribution, and as n and % for categorical variables. In comparing those patients with spirometry documentation of airways obstruction consistent with COPD (i.e., a forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio (FEV1/FVC) < 0.70)[13] to those who did not meet this criterion, Chi-square analyses were used with categorical variables (gender, race, low SES, hospitalizations). For those variables with a normal distribution (age, FEV1 percent-predicted), T-tests were used. For those without a normal distribution (FVC, months of follow up, and CCI score), Wilcoxon signed rank tests were used.

The effect of CCI on mortality was analyzed in a forward stepwise Cox Proportional Hazards analysis as a continuous variable in a model that also included the above-listed factors as covariates. In addition, a second Cox regression model was run, with CCI scores categorized into the following: CCI = 1 (COPD only, without comorbidity); CCI =2 (1 comorbid condition); CCI = 3 (2 comorbid conditions); and CCI ≥ 4 (3 or more comorbid conditions). These categorizations were close to quartiles.

Results

Of the 200 patients studied, 118 (59%) met the accepted spirometry criterion for airflow limitation associated with COPD (FEV1/FVC < 0.70). Of those meeting spirometric criteria for COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD),[9] airflow limitation was categorized as mild in 14%, moderate in 49%, severe in 29%, and very severe in 8%. Patient demographics, FEV1 percent-predicted, all-cause hospitalizations in the preceding year, CCI scores, CCI categories, follow up intervals, and mortality for the total group and those with and without documented airflow limitation are given in Table 1. For the entire group, 55.5% were female, 50.5% were Black/African American, and the FEV1 was 62.2 ± 18.1 percent-predicted. Mean all-cause hospitalizations in the preceding 12 months was 0.72 ± 1.25 (range, 0 to 10) and the median and IQR were: 0.0 (IQR 0.0 – 1.0). There was skewing of this variable toward the zero-hospitalization end of the curve: zero (n = 117), 1 (n = 50), 2 (n = 21), 3 or more (n = 12). Overall, approximately 70% of patients had at least 1 comorbid condition in addition to COPD (CCI>1). Other than CCI category and FEV1 percent-predicted values, the two groups did not differ with respect to any of the other variables tested.

The median CCI score was 2.0 (IRQ 1.0 – 4.0, range 1 to 12). Note that every patient in this sample had a CCI score of at least 1 (COPD only). The distribution of CCI scores is given in Figure 1. A listing of individual comorbid conditions contributing to the CCI for those with and without the FEV1/FVC criterion are given in Table 2.

For the total group (n=200), mortality was 8.5% and 20% at 3 and 5 years, respectively. Using proportional hazards modeling, we compared mortality by the presence (n=118) or absence (n=82) of spirometry confirmation of airflow limitation. Since airflow limitation did not significantly predict mortality (p = 0.67, log rank), we used the total group (n=200) for subsequent analyses.

In univariate analyses, age, sex, race, and SES and GOLD spirometric severity classifications were not related to mortality, but the number of all-cause hospitalizations in the previous 12 months, expressed as a continuous variable, was predictive (HR 1.26, 95% CI 1.08 to 1.47, p = 0.02). The CCI, expressed as a continuous variable, also significantly predicted mortality in univariate analysis: hazard ratio (HR) = 1.38, 95% CI 1.27 to 1.50, for each unit increase in the score (p < 0.0001). For this, each unit increase represents one additional comorbid condition in the CCI.

In multivariable Cox proportional hazards modeling of mortality, including patient demographics, comorbidity, and hospitalizations as independent variables, only CCI and hospitalizations in the preceding 12 months (each expressed as continuous variables) significantly predicted mortality (p < 0.0001 and 0.017, respectively). All other covariates not meeting a priori statistical criteria were dropped from the model.

The results of the second multivariable Cox proportional hazards model, using the CCI *category* and number of hospitalizations as a covariates, are depicted in Table 3 and Figure 1. Those patients in the CCI ≥ 4 category had significantly higher hazard ratios for mortality than those in the three lesser categories, with an approximate 10-fold risk of dying than in categories 1 and 2 (HR 9.80, 95% CI 3.80 to 25.00, HR 10.31, 95% CI 3.68 to 29.41, respectively), and an approximate 6-fold increased risk of dying compared to those in category 3 (HR 6.21, 95% CI 2.21 to 17.54).

Discussion

The one-year and five-year all-cause mortality in the patients with a clinical diagnosis of COPD in our study were 8.5% and 20%, respectively. This five-year percentage approximates the 24% and 28% and mortality rates for this disease published elsewhere.[2,14] Of note, the FEV1, expressed as percent-predicted, did not predict mortality in our study, even when patients without demonstration of airways obstruction (FEV1/FVC < 0.70) were excluded from the analysis. While the FEV1 has been recognized as a predictor of mortality in COPD since at least 1986,[15] it has become clear that, in this disease with prominent systemic effects and comorbid conditions, other factors also affect prognosis.[16] Our study provided evidence that the CCI score

Table 1. Patient characteristics.

	Total	FEV1/FVC < 0.70	FEV1/FVC ≥ 0.70	p
n	200	118	82	
Female (n, % of total)	111 (55.5)	60 (51)	51 (62)	0.11
Age (years) (mean ± SD)	62.2 ± 9.7	62.5 ± 10.1	61.7 ± 9.2	0.58
Black/African American (n, % of total)	101 (50.5)	63 (53.4)	38 (46.3)	0.33
Low SES (n, % of total)	187 (93.5)	109 (92.4)	78 (95.1)	0.44
FEV1 percent-predicted (mean ± SD)	62.2 ± 18.1	57.0 ± 18	70.3 ± 15.1	< 0.0001
FVC percent-predicted (median, IQR)	74.0 (63.0 - 87.0)	74.5 (63.0 - 91.0)	72.5 (63.0 - 80.0)	0.06
Hospitalizations previous yr (mean ± SD)	0.72 ± 1.25	0.75 ± 1.17	0.66 ± 1.35	0.59
≥ 1 hospitalization previous yr (n, %)	83 (41.5)	55 (46.7)	28 (34.2)	0.08
CCI (median, IQR)	2.0 (1.0 - 4.0)	2.0 (1.0 - 4.0)	2.0 (2.0 - 4.0)	0.30
CCI category				0.01
1 (n, %)	59 (29.5)	43 (36.4)	16 (19.5)	
2 (n, %)	50 (25.0)	21 (17.8)	29 (35.4)	
3 (n, %)	31 (15.5)	19 (16.1)	12 (14.6)	
≥ 4 (n, %)	60 (30.0)	35 (29.7)	25 (30.4)	
Follow up (months) (median, IQR)	69.1 (50.6 - 84.5)	68.6 (48.8 - 83.1)	69.3 (53.3 - 87.6)	0.34
Died during follow up period (%)	51 (25.5)	28 (23.7)	23 (28.0)	0.49

SD: standard deviation; IQR: interquartile range.

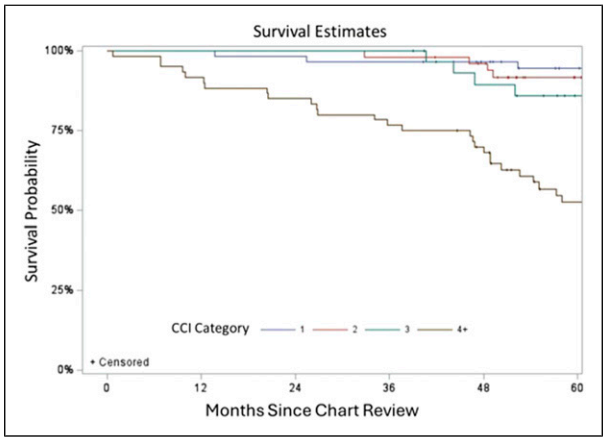

Figure 1. Kaplan-Meier Survival Curve Depicting relationship between CCI Category and Survival. Since the CCI includes COPD as a comorbid condition in its algorithm, the number of non-COPD comorbid conditions is 1 fewer in each category (e.g., CCI category of 1 has no additional comorbid conditions).

obtained via electronic record review of those with a clinical diagnosis of COPD was a strong predictor of all-cause mortality in outpatients with this disease. This was evidenced by a hazard ratio of all-cause mortality in those with 3 or more comorbid conditions (compared to none) of 9.80 (95% CI 3.80 to 25.00).

The Charlson Comorbidity Index was created in the 1980's to identify those medical comorbid conditions that predict an adjusted mortality risk at one year.[17] Higher scores on this instrument were subsequently found to be associated with increased mortality risk out to several years for a number of different primary disease states.[7] Our study adds to this information by demonstrating that the CCI score derived from a record review of electronic medical records of outpatients with clinical diagnosis of COPD was a stronger predictor of all-cause mortality out to 5 years than patient demographics or our two markers of COPD disease severity, preceding all-cause hospitalizations and degree of airflow limitation. While we utilized a look-back record review to measure the CCI, the feasibility of using ICD-9 or ICD-10 codes to this end has been demonstrated,[7,12,18,19,20] indicating that this instrument could readily be incorporated into algorithms predicting mortality in the outpatient setting.

Importantly, we demonstrated a non-linear relationship between increasing CCI and mortality: while one additional CCI comorbid condition was not related to prognosis and 2 conditions was not statistically significant, those with 3 or more non-COPD comorbid conditions (CCI ≥ 4) had almost 10 times the risk of dying over the study period compared to those with no non-COPD comorbidity.

Our study inclusion criteria included ICD-10 codes indicating a primary clinical diagnosis of COPD and at least one spirometry measurement. Interestingly, 82 patients (41%) of our sample – even though all had spirometry - did not have the presence of fixed airflow limitation (FEV1/FVC < 0.70) required for confirmation of the diagnosis.[9] The absence of airflow limitation confirmation of COPD in a substantial percentage of patients with this clinically diagnosed disease has been documented. For example, in a record review of

Table 2. Comorbid conditions comprising CCI scores.

CCI comorbidity	FEV1/FVC < 0.70	FEV1/FVC ≥ 0.70	P
Myocardial infarction	8 (6.8)	6 (7.3)	0.29
Congestive heart failure	25 (21.2)	22 (26.8)	0.19
Peripheral vascular disease	9 (7.6)	6 (7.3)	0.60
Cerebral vascular disease	9 (7.6)	5 (6.1)	0.29
Dementia	2 (1.7)	4 (4.9)	0.41
Connective tissue disease	12 (10.2)	9 (11.0)	0.43
Peptic ulcer disease	6 (5.1)	6 (7.3)	-
Mild liver disease	3 (2.5)	3 (3.7)	-
Moderate or severe liver disease	1 (0.8)	3 (3.7)	0.32
Diabetes without end organ damage	32 (27.1)	28 (34.1)	0.27
Diabetes with complications	10 (8.5)	14 (17.1)	0.41
Hemiplegia or paraplegia	1 (0.8)	0 (0.0)	-
Renal disease	9 (7.6)	7 (8.5)	0.62
Any tumor, leukemia, or lymphoma	15 (15.7)	9 (11.0)	0.22
Metastatic solid tumor	3 (2.5)	0 (0.0)	-
HIV/AIDS	6 (5.1)	2 (2.4)	0.16

Diagnoses based on references.[11,7]
Numbers in parentheses represent the percentages in each category.
Score weights for each variable are given in text.

Table 3. Comparisons of non-COPD CCI categories with respect to morality risk.

	Mortality risk	
Category comparison	HR	95% CI
CCI 2 vs. 1	0.95	0.25 to 3.54
CCI 3 vs. 1	1.57	0.42 to 5.86
CCI 4+ vs. 1	9.80	3.80 to 25.00
CCI 3 vs. 2	1.66	0.42 to 6.67
CCI 4+ vs. 2	10.31	3.68 to 29.41
CCI 4+ vs. 3	6.21	2.21 to 17.54

HR: hazard ratio; CI: confidence interval.
Since COPD is one of the comorbid conditions included in the CCI, those in the CCI 1, 2, 3 and 4 categories had 0, 1, 2 and ≥ 3 comorbid conditions, respectively.

Swedish patients with a clinical diagnosis of COPD, an FEV1/FVC < 0.70 was present in only 34% of their sample with post-bronchodilator spirometry available.[21]

In our study, the groups with and without spirometrically confirmed airflow limitation did not differ with to respect to age, sex, race, socioeconomic status, CCI, and all-cause hospitalizations in the preceding year. Since hospitalizations did predict mortality in our analysis, this suggests that it was a more robust predictor of this unfavorable outcome in our sample of outpatients with clinical diagnoses of COPD.

The relationship between Charlson comorbidity and survival in COPD has had limited investigation. In one study, the CCI was determined to be predictive of in-hospital and 1-year mortality in 4202 individuals with COPD who had their first hospitalization for an exacerbation of this disease.[22] While this instrument demonstrated that comorbidity predicted mortality in this specific situation, to our knowledge, only two other studies evaluated the CCI as a potential mortality predictor variable when measured in outpatients with COPD.[23,24]

In the first of these studies, Pinto-Plata and colleagues[23] used the CCI as a covariate in their primary analysis relating changes in the six-minute walk distance to 1-year mortality in COPD patients who had been recruited for the study from an outpatient setting. Cardiac disease, malignancies, and diabetes were most common in their analysis, as were in ours. In their multivariable analysis that also included covariates of age, FEV1, six-minute walk distance and body-mass index, and the CCI, the six minute walk distance strongly predicted mortality, but the CCI did not ($p = 0.10$). In this study, the patients likely had greater airflow limitation than ours, and as COPD severity increases, patients are more likely to die because of the disease rather than with the disease.[8,25] Also, these researchers included the six-minute walk distance in their multivariate analysis, and as this is a very potent factor associated with mortality in COPD,[26] its inclusion in the model may have overwhelmed the significance of the other factors.

The second study[24] evaluating the CCI as a predictor of mortality in COPD involved a retrospective review of 17,745 primary care patients in Sweden who had COPD (based on ICD-10 Coding[20]) that analyzed multiple variables as potential predictors of all-cause mortality over an approximately 10-year study period. CCI expressed as a continuous variable at baseline had a hazard ratio of 1.31 (95% CI 1.29 to 1.34) and 1.12 (95% CI 1.09 to 1.14) in

univariate and multivariable Cox Proportional Hazards analysis, respectively. The mean CCI score of 0.86 was considerably lower than in our sample (3.08), possibly representing differences in practices, since patients in the former were recruited from primary care centers and ours from internal medicine and pulmonary clinics. Additionally, the method of obtaining data from chart review likely identifies more components of the CCI than from methods based on coding,[27] possibly explaining some of this difference. Despite the differences in CCI, the hazard ratio of 1.31 predicting all-cause mortality in their univariate analysis is remarkably close to ours, which was 1.38.

Our study has several limitations. First, 94% of our sample had low SES, as indicated by Medicaid or no insurance, which reflects or inclusion of patients in medical and pulmonary clinics at a community hospital. This would potentially limit applicability of our results to a more diverse population since individuals with markers of low SES have a higher comorbidity burden,[28] although – at least in one study of older adults in Ontario, Canada[29] - no increase in mortality. Second, as mentioned above, a sizeable percentage of patients with clinical diagnoses of COPD did not have confirmation of airflow limitation by spirometry. However, the presence of airflow limitation (FEV1/FVC < 0.70) was somewhat surprisingly not a factor in affecting prognosis in those patients who met our inclusion criterion of a clinical diagnosis of COPD, so we believe there is justification for including them in the analysis. CCI was such a strong factor predicting mortality in our sample that the effect of airflow limitation may have been overwhelmed. Further analysis with a larger sample size would be needed to determine whether airflow limitation significantly adds to the CCI and hospitalization history as predictors of mortality in this group. Third, our method of using State of Connecticut vital statistics database information will miss those who moved elsewhere and died outside of this jurisdiction. However, we believe this potential bias is rather small. Finally, the CCI fails to take into account some important and commonly present comorbid categories, such as depression. It is not known whether or not adding them to the analysis may improve mortality prediction.

Our study contributes to the relationship between comorbidity and prognosis in COPD by demonstrating what appears to be a non-linear dose-response relationship between CCI categories and mortality risk, with no significant increase in mortality with 1 or 2 comorbid conditions (excluding COPD) compared to none (HR 9.92, 95% CI 0.25 to 3.54 and HR 1.57, 95% CI 0.42 to 5.85, respectively), but a with marked increase in risk with 3 or more conditions compared to none (HR 9.80, 95% CI 3.80 to 25.00). This supports the statement by Sin and colleagues in their review of comorbidity in COPD that the impact of the Charlson on mortality is probably exponential in nature.[25]

In summary, in our analysis of 200 outpatients with a clinical diagnosis of COPD, the Charlson Comorbidity Index (CCI) score from record review strongly predicted subsequent all-cause mortality out to approximately 5 years. In multivariable analysis including age, sex, socioeconomic status, race, FEV1 percent-predicted, and number of all-cause hospitalizations in the preceding year, only the CCI and hospitalizations were significant predictors of this outcome. The relationship between CCI scores and mortality appears to be non-linear: the presence of 1 or 2 non-COPD comorbid conditions did not significantly predict mortality, but those patients with 4 or greater had an approximately 10-fold increase in mortality risk.

The clinical implication of our study is that the CCI may prove useful in evaluating COPD patients. Sundararajan it may allow clinicians and health care administrators to focus scarce medical resources on those with the worst prognosis.

Author contributions

Kevin Ly: Protocol design, data collection, data evaluation, editing; Dorothy Wakefield: Statistical analysis, editing; Richard ZuWallack: administrative, protocol design, editing.

Declaration of conflicting interests

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IRB statement

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