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The relationship of Charlson comorbidity index with stent restenosis and extent of coronary artery disease

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Abstract: *Objectives:* The objective of this study is to investigate the effect of comorbid conditions [Charlson comorbidity index (CCI)] on stent restenosis who underwent coronary angioplasty earlier. *Methods:* Patients were divided into two groups; patients with critical restenosis [recurrent diameter stenosis >50% at the stent segment or its edges (5-mm segments adjacent to the stent) (Group 1; $n = 53$, mean age: 63.8 ± 9.9 years)] and patients with no critical restenosis [<50% obstruction (Group 2; $n = 94$, mean age: 62.1 ± 9.1 years)]. The CCI and modified CCI were used for the presence of comorbid conditions. The Gensini scoring system was used to assess the extent of coronary artery disease (CAD). *Results:* Group 1 had a significantly greater CCI and modified CCI score compared to Group 2 (7.1 ± 3.7 vs. 5.6 ± 1.6, $p = 0.006$; 6.9 ± 3.6 vs. 4.5 ± 1.5, $p = 0.008$, respectively). There was a weak correlation, albeit significant, between the modified CCI score and restenosis percentage ($r = 0.29$, $p < 0.001$; $r = 0.25$, $p = 0.003$, respectively). *Conclusions:* In conclusion, the CCI score is greater among patients with stent restenosis than those without. CCI score is higher among patients with a more diffuse CAD than with a milder disease extent.

Keywords: coronary artery disease, Charlson score, restenosis, Gensini, comorbidity

Introduction

Ischemic heart disease is one of the leading causes of death both worldwide and in Turkey. As the life expectancy continues to climb, the incidence of coronary artery disease (CAD) rises, which increases the number of patients undergoing percutaneous coronary intervention (PCI) [1, 2]. Restenosis and thrombosis are potentially fatal complications of coronary stenting with a recognized multifactorial etiology. In addition to procedural factors, such as inadequate antiplatelet therapy, lesional factors, large tissue injury, incomplete stent apposition, and inadequate stent apposition, patient-specific factors, such as comorbidities, precipitate stent restenosis [3].

It is known that comorbid conditions increase the morbidity and mortality to a greater extent than the ischemic heart disease *per se* [4, 5]. Considering various comorbidities accompanying ischemic heart disease in many patients undergoing PCI, it is unimaginable that comorbid conditions do not affect short- and long-term success of stenting procedure [6]. Charlson comorbidity index (CCI) is a measure of comorbidity burden that enables the assessment of the prognostic significances of various clinical conditions on the basis of their number and each one's prognostic impact. CCI is an index whose role has been investigated in various clinical conditions and whose importance as a prognostic indicator has been shown [7]. This study investigated the relationship between comorbid conditions and stent restenosis in patients who underwent coronary angiography for stable CAD after undergoing a previous PCI procedure in the past. The correlation of comorbid conditions to the extent of CAD was also studied.

Materials and Methods

Patient selection

This study included a total of 147 patients (41 women and 106 men; mean age: 62.7 ± 9.4 years) who had previously undergone a coronary intervention procedure with stent implantation after having been presented with acute coronary syndrome and who underwent coronary angiography for any reason. A detailed patient history was obtained from each patient. The demographic characteristics, cardiovascular risk factors, blood pressure, and heart rate during the coronary angiography were recorded. The detailed information about previous coronary angiography and stenting procedures (stent type, brand, size, and dilatation pressure in atmosphere) was obtained and recorded. The patients gave venous blood samples of urea, creatinine, lipid panel, C-reactive protein, and whole blood count after 8 h of fasting.

The patients who had undergone a previous coronary artery bypass operation, presented with acute myocardial infarction, refused to participate, and who had undergone stent implantation less than 4 months earlier were excluded.

All patients were examined with transthoracic echocardiography 1 day after the coronary angiography procedure. Left ventricular size, left ventricular diastolic function, pulmonary artery pressure, and left ventricular ejection fraction (EF) using the modified Simpson method were calculated and recorded.

Ethics

The local ethical committee of Faculty of Medicine, Bulent Ecevit University approved the study. All participants gave informed written consent.

Charlson comorbidity index (CCI)

CCI is a widely used mortality assessment model in which the varying impact of various chronic conditions on 1-year mortality is considered. Necessary information to calculate the CCI was obtained through the history taken during admission. The CCI was then calculated by the summation of the comorbidity scores of each condition as shown in *Table I* [7].

The CCI scores were obtained during coronary angiography and only those comorbidities that had been present, since the time of stent implantation were considered. The CCI score was calculated for each participant. The modified CCI score was calculated by substracting 1 point from the original CCI score for CAD patients with an EF <40%. Both scoring systems were considered

Table I | Determinants of Charlson comorbidity index

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral disease (includes aortic aneurysm ≥6 cm
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastasis (exclude if >5 years from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

for statistical analyses. The CCI was rated as mild (score: 1–2), moderate (score: 3–4), and severe (score: ≥5).

Coronary angiography

Coronary angiography was performed in all patients. All angiograms were taken using a monoplane angiographic system (Artis zee, Siemens Erlangen, Germany). Selective coronary angiograms were carried out with 6F Judkins catheters advanced through femoral artery. Patients were divided into two groups; patients with critical stent restenosis [recurrent diameter stenosis >50% at the stent segment or its edges (5-mm segments adjacent to the stent)] and patients with no critical restenosis <50% obstruction. The percentage of the coronary stenoses was agreed by two separate operators. As a result, 53 patients had critical restenosis (15 F; mean age: 63.8 ± 9.9 years) and 94 had non-critical restenosis (27 F; mean age: 62.1 ± 9.1 years). The ratio of drug eluting stent (DES) restenosis was 19 (36%) in Group 1 and 37 (41%) in Group 2. Most of the stent implanted lesions were isolated lesions, where there were small number of left main and bifurcation lesions.

The Gensini scoring system was used to assess the extent of CAD as mild, moderate, and severe. It was quantified by multiplying the severity coefficient, based on the severity of vessel narrowing (reductions of 25%,

50%, 75%, 90%, 99%, and complete occlusion was assigned Gensini scores of 1, 2, 4, 8, 16, and 32, respectively) by a coefficient determined by the functional importance of the myocardial area supplied by the stenosed vessel. A Gensini score of 54 or greater was accepted as high, a score of 24–54 as moderate, and a score below 24 as low score [8]. Then, low-, moderate-, and high-score groups were categorized, which were individually statistically analyzed except for the control group and the severe CAD group. The low Gensini score group contained 82 patients (27 F; mean age: 61.8 ± 9.5 years), the moderate-score group contained 40 patients (11 F; mean age: 64.2 ± 9.2 years), and the high-score group contained 25 patients (9 F; mean age: 63.4 ± 9.1 years). SYNTAX score was also calculated in addition to the Gensini score for each patient. Most of the lesions were isolated lesions, where there were small number of left main and bifurcation lesions.

The total SYNTAX score was calculated from the baseline angiogram by summating the individual score of each separate lesion using a SYNTAX score algorithm that is found on the SYNTAX website (www.syntaxscore.com). A SYNTAX score of 22 or below was categorized as low, 23–32 as intermediate, and 32 or above as a high score.

Statistical analysis

All statistical analyses were carried out using SPSS for Windows 13.0. The Kolmogorov–Smirnov test was used to test the normality of distribution of quantitative data. Descriptive statistics for numerical variables were expressed as mean $\pm$ SD, while categorical data were reported as n (%). The χ^2 test and Fisher's exact χ^2 test were used to compare categorical variables between the groups. The comparison of continuous variables between the control and critical CAD groups was performed by the independent sample test and analysis of variance, when the assumptions of parametric test were met and by Mann–Whitney U and Kruskal–Wallis tests when the assumptions of parametric test were not met. The relationship between CCI score and Gensini scores was analyzed by correlation analysis. The statistical significance was set at $p < 0.05$ and the confidence interval at 95%.

Results

Patients were divided into two groups: Group 1, 53 of the patients had significant restenosis (15 F; mean age: 63.8 ± 9.9 years) and Group 2, 94 had non-significant restenosis (27 F; mean age: 62.1 ± 9.1 years). The critical CAD group and the control group were similar in terms of age, systolic and diastolic blood pressure, heart rate, body mass index, gender, EF, diabetes mellitus, hypertension, hyperlipidemia, familial history of CAD, and smoking history (Table II). Glucose, urea, creatinine, and lipid panel were also comparable in both groups (Table II). The ratio of DES restenosis was statistically non-significant between the Groups 1 and 2 [19 (36%) and 37 (41%), respectively; $p = 0.53$].

Group 1 had a significantly greater CCI score and modified CCI score compared to Group 2 (Table II). Group 1 had a significantly greater Gensini and SYNTAX scores than Group 2 (39.6 ± 25.8 vs. 20.1 ± 21.3, $p < 0.001$; 15.8 ± 7.6 vs. 11.8 ± 8.2; $p = 0.004$, respectively). There was a weak correlation, albeit significant, between the modified CCI score and restenosis percentage ($r = 0.29$, $p < 0.001$; $r = 0.25$, $p = 0.003$, respectively). CCI and modified CCI scores were weakly but significantly correlated with the presence of severe stenosis ($r = 0.22$, $p = 0.01$; $r = 0.21$, $p = 0.01$, respectively). Receiver operating characteristic (ROC) analysis revealed that a Charlson score greater than 8 may predict the presence of severe restenosis with 25% sensitivity and 98% specificity ($p = 0.01$, area under curve: 0.625; Fig. 1).

When the groups were categorized by the Gensini score as low, intermediate, and severe, the CCI scores were significantly different between the groups (5.5 ± 2.1 vs. 6.8 ± 3.6 vs. 6.8 ± 2.5; $p = 0.02$). There was a weak correlation, albeit significant, between the CCI and the Gensini scores ($r = 0.25$, $p = 0.003$).

The groups categorized by the Charlson score as intermediate (27 patients) and severe (116 patients) were compared (the mild group contained four patients and was therefore excluded from the statistical analysis). The Gensini score was significantly greater in the severe group compared to the intermediate group (30.4 ± 25.9; $p = 0.01$). SYNTAX score was similar between the groups (14.1 ± 8.3 vs. 11.7 ± 6.4; $p = 0.11$).

Discussion

The main result of this study is that the incidence of stent restenosis climbs as the number of comorbid conditions increases. Among the patients with CAD, CCI score is increased in those with diffused CAD. Although our correlation analysis showed a weak correlation, it can be concluded that as the comorbidity burden increases, CAD extent and restenosis percentage parallely increase.

Stent restenosis is one of the major complications after PCI and poses a challenge for interventional cardiologists. Despite technological advances in stents and interventional techniques, stent restenosis is far from being totally eliminated [9]. While the pathogenesis of restenosis following PCI without stenting is thought to mainly include vessel remodeling and elastic recoil, it is thought to result from neointimal proliferation and a newly occurring atherosclerotic process called neoatherosclerosis following PCI with stenting [10].

Table II Demographic, laboratory parameters, and comorbidity scores of the groups

	Critical stenosis (+) (n = 53)	Critical stenosis (−) (n = 94)	p
Age (years)	63.8 ± 9.9	62.1 ± 9.1	0.28
Gender (male)	67	38	0.93
BMI (kg/m²)	29.5 ± 6.9	27.8 ± 5.2	0.11
Systolic blood pressure (mmHg)	131.4 ± 28.8	137.8 ± 19.6	0.26
Diastolic blood pressure (mmHg)	80.8 ± 16.8	80.4 ± 19.6	0.94
Heart rate (beat/min)	80.9 ± 15.0	83.7 ± 15.2	0.54
Hypertension (n)	45	74	0.28
Diabetes (n)	39	30	0.08
Smoking (n)	18	8	0.39
Family history of CAD	2	4	0.50
Blood glucose (mg/dl)	145.8 ± 55.8	136.9 ± 59	0.40
LDL-C (mg/dl)	108.4 ± 42.9	109.3 ± 43.3	0.91
HDL-C (mg/dl)	39.9 ± 8.7	40.1 ± 7.8	0.89
TC (mg/dl)	189.4 ± 54.9	184.5 ± 49.4	0.60
TG (mg/dl)	193.0 ± 109.6	209.2 ± 166.7	0.54
Stent duration (months)	47.6 ± 43.3	33.7 ± 33.3	0.07
Stent type (DES, n)	19	39	0.53
CCI	7.1 ± 3.7	5.6 ± 1.6	**0.006**
Modified CCI	6.9 ± 3.6	4.5 ± 1.5	**0.008**

BMI: body mass index; CAD: coronary artery disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; DES: drug eluting stent; CCI: Charlson comorbidity index. Bold values of CCI and modified CCI represent $p < 0.01$
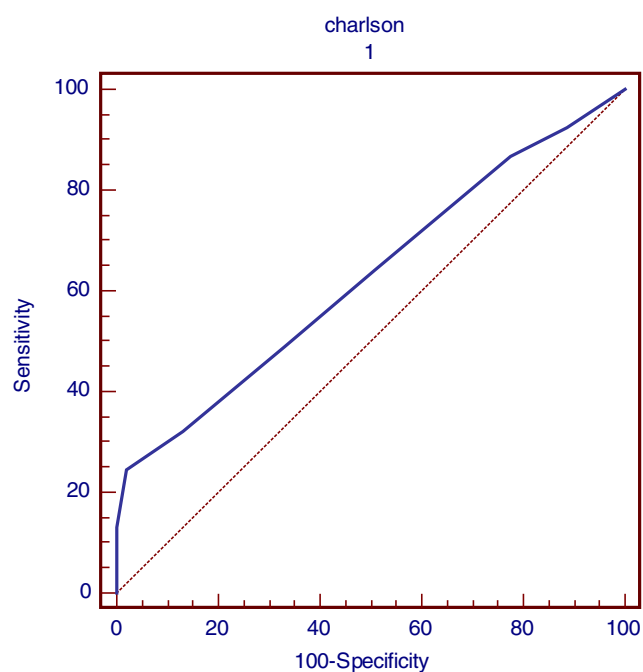
Fig. 1. ROC curve for relation of Charlson score with severe stent restenosis

As the population ages, there occurs an increase in the prevalence of chronic medical conditions, such as hypertension, vascular disorders, arthritis, and cancer. It is known that more than 60% of persons older than 60 years suffer from two or more chronic disorders [11]. Former studies have indicated that the morbidity burden of comorbidities is high in a sizable portion of patients with coronary heart disease, and many others have reported the presence of at least one comorbid condition in more than half of the patients [12, 13]. Several studies have been conducted on CAD and comorbidities, and the two have been shown to be closely interrelated. Chirinos et al. [14] prospectively followed 305 patients with CAD and showed that comorbidity indexes may predict long-term mortality. Similarly, Nunez et al. [15] demonstrated that the CCI score determined during infarction may predict 30-day and 1-year mortality among a large patient population treated for acute myocardial infarction. One of the studies that examined the relationship of CCI with long-term mortality; Nobori-2 conducted by Mamas et al. [16] confirmed that the CCI score above 2 may be predictive of 30-day mortality in 3,067 patients followed after PCI. Some regional registry studies have concluded that diabetes, peripheral arterial disease, heart

failure, and chronic renal failure are among the most important components of contemporary risk-scoring systems developed for PCI [17, 18]. Comorbidities not only affect the prognosis of ischemic heart disease, but also affect diagnosis, quality of life, and the selection of treatment modality [19]. This study also revealed that the CCI and modified CCI scores were significantly greater among the patients with restenosis in both groups with similar atherosclerotic risk factor profiles. Although the correlation was weak, the rate of restenosis and restenosis percentage were significantly increased as the CCI and modified CCI scores increased. These results suggest that comorbid conditions are as effective as procedural success, conventional cardiovascular risk factors, and stent models for stent patency after PCI. ROC analysis showed that stent restenosis may lesser develop in patients with a Charlson score less than 8.

Gensini score is one the most commonly employed scoring systems for showing the severity of CAD, which accounts for the cumulative effect of multiple stenoses in addition to the disease's geographic location and luminal narrowing [20]. Gensini score not only shows the number of stenosed vessels, but also the percentage and anatomic localization of great vessel stenosis. This scoring is frequently used to quantify the extent and severity of CAD [21]. Gensini is a scoring system that has been used to predict the diffuseness of CAD in various patient groups or various markers. In this study, there was a significant difference between the groups formed on the basis of Gensini score with respect to the CCI score. The same did not apply for groups formed by the severity of the SYNTAX scores. This suggests that patients with a greater comorbidity burden had a more diffuse CAD.

Study Limitations

One of the main limitations of this study is the inclusion of a relatively low number of patients for CAD, which is a prevalent disorder. The other limitation was the weak correlation studies. When we evaluated our results, we interpreted these results only a probability. To our opinion, had our number of subjects been greater, stronger correlations would have been obtained.

In conclusion, the CCI score, a quantified scoring system of comorbid conditions, is greater among the patients with stent restenosis than those without. CCI score is greater among patients with a more diffused CAD than with a milder disease extent. Patients with a Charlson score less than 8 may have lower stent restenosis. A high comorbidity burden appears to be related to the obstruction of a previously implanted stent. Comorbidities should also be addressed in addition to standard antiplatelet therapies and risk factor modification in efforts against stent restenosis.

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