

Clinical Predictors & Risk Stratification of Unstable Angina

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Abstract:

Background: Detection of high risk patients with unstable angina is one of the important steps in saving their lives and preventing possible major cardiovascular events that can affect their morbidity and mortality.

Objectives: This study had been designed to estimate the effect of age, gender and different clinical parameters on the short term outcome of patients with unstable angina.

Methods: This study is a prospective study that enrolled 100 patients with unstable angina. The included patients had been randomly selected from those who had been admitted to the Coronary Care Unit of Al-Yarmouk Teaching Hospital during the period between the 1st of July and the 31st of December 2003. Each patients included in this study had been followed up for 72 hours to 2 weeks according to the period of admission in the hospital, searching for any mortality, new or recurrent myocardial infarction or recurrent ischemia that necessitate the referral to intervention cardiology center. Unfortunately there was no facility for catheterization in the hospital and no one of the included patients referred back to the hospital to know the results of catheterization. All of the patients underwent thorough physical examination. All of them had been sent for ECG, chest X-ray and echocardiographic examination.

Results: All cause mortality had been identified only in those patients whose age were 65 year old or older (6 patients, 6% of the whole sample). 66.7% of deaths (4 deaths) were observed among class III patients (only 26.3% of class III patients had relieved from chest pain) i.e. angina at rest and acute.

Conclusions: All cause mortality, frequency of new or recurrent myocardial infarction and recurrent ischemia were increased with the increase in the severity class. According to the clinical circumstances related to unstable angina, secondary unstable angina i.e. class A was the least frequent type (only 5 patients, 5% of the sample). According to the intensity of therapy, the worse outcome had been observed among those patients who are under the maximally tolerated doses of anti-ischemic drugs.

Introduction

Unstable angina accounts for more than 1 million hospital admissions annually⁽¹⁾, 6 to 8 percent of patients with this condition have non-fatal myocardial infarction or die within the first year after the diagnosis⁽²⁻³⁾. Various definitions of unstable angina have been proposed, but in 1989, Braunwald devised a classification system to ensure uniformity of categorization, as well as diagnostic and prognostic information⁽⁴⁾. This system is used to classify angina according to the severity of the clinical manifestation, defined as acute angina while at rest (within the 48 hours before presentation), subacute angina while at rest (within the previous month but not within the 48 hours before presentation), or new onset of accelerated (progressively more severe) angina; the clinical circumstances in which unstable angina develops, defined as either angina in the presence or absence of other conditions (e.g., anemia, fever, hypoxia, tachycardia, or thyrotoxicosis) or angina within two weeks after an acute myocardial infarction; and whether or not electrocardiographic abnormalities are present. Given the heterogeneity of the clinical manifestations of unstable angina, it is not surprising that the prognosis is quite variable⁽⁵⁾.

Two major challenges in a patient with suspected unstable angina are establishing the diagnosis and risk stratification. Successful separation of low and high risk individuals permits the discharge of low risk patients after an initial evaluation, and the rapid triage of high risk patients to intensive management and/or invasive diagnostic and therapeutic procedures. Clinical risk stratifications correlates with the extent of disease⁽⁶⁻⁷⁾. All patients considered to have unstable angina require close monitoring because of the risk of progressing to myocardial infarction. Thus it is recommended to admit such patients to the hospital where the evaluation can be performed under controlled setting⁽⁵⁾.

This study had been designed to estimate the frequency of different age groups and its effect on the outcome of patients with unstable angina, to find the sex distribution of patients with unstable angina and assess any effect of gender on the outcome of unstable angina, and to find the frequency of different risk factors and identify any combination between them and assess the effect of these risk factors and their combination on the outcome of unstable angina.

Patients & Methods

This study is a prospective study that enrolled 100 patients with unstable angina. The included patients had been randomly selected from those who had been admitted to the Coronary Care Unit of Al-Yarmouk Teaching Hospital during the period between the 1st of July and the 31st of December 2003. Each patients included in this study had been followed up for 72 hours to 2 weeks according to the period of admission in the hospital, searching for any mortality, new or recurrent myocardial infarction or recurrent ischemia that necessitate the referral to intervention cardiology center. Unfortunately there was no facility for catheterization in the hospital and no one of the included patients referred back to the hospital to know the results of catheterization. All of the patients underwent thorough physical examination. All of them had been sent for ECG, chest X-ray and echocardiographic examination.

Results

This study had enrolled 100 patients, who can be divided into 4 main groups:

- 1- Those patients who had their chest pain relieved by medical therapy and discharges from the hospital with full or partial improvement, this group of patients included 62 patients (62% of the whole sample).
- 2- Those who had recurrent ischemia during period of hospital admission that required referral to cardiac intervention center out of the hospital for angiography and angioplasty, this group included 21 patients (21% of the whole sample).
- 3- Those who acquired new or recurrent myocardial infarction during the period of hospital admission, this group included 11 patients (11% of the whole sample).
- 4- Those who had died during the period of hospitalization, and included 6 patients (6% of the whole sample).

Age of the patients

The patients included in this study had an age ranged between 36-80year-old (56.35 ± 11.34 year old). 12 and 41 patients (12 and 41% of the total sample) were under the age of 55 and older than 65 year old, respectively.

- ✓ All cause mortality had been identified only in those patients whose age were 65 year old or older (6 patients, 6% of the whole sample).
- ✓ 72.7% of those who had new or recurrent myocardial infarction during the hospitalization period were 65 year old or older (8 patients).
- ✓ 61.9% of those with recurrent ischemia necessitating referral for cardiac center were 65 year old or older (13 out of 21 patients).
- ✓ 77.4% of those with improvement in their chest pain were younger than 65 year old (48 out of 62 patients). (see Table-1).

Table-1: Patients' distribution according to their demographic features.

| Demographic feature | | All cause mortality (n =6) | | New or recurrent MI (n=11) | | Recurrent ischemia (n=21) | | Improved (n=62) | |
|---------------------------------------|-----------------------------|----------------------------|------|----------------------------|------|---------------------------|------|-----------------|------|
| | | No. | % | No. | % | No. | % | No. | % |
| Age (yrs) | 35-44 (n=4) | 0 | 0 | 0 | 0 | 2 | 9.5 | 2 | 3.2 |
| | 45-54 (n=8) | 0 | 0 | 2 | 18.2 | 3 | 14.3 | 3 | 4.8 |
| | 55-64(n=47) | 0 | 0 | 1 | 9.1 | 3 | 14.3 | 43 | 69.4 |
| | 65-74(n=21) | 2 | 33.3 | 3 | 27.3 | 5 | 23.8 | 10 | 16.1 |
| | 75-84(n=20) | 4 | 66.7 | 5 | 45.4 | 8 | 38.1 | 17 | 27.4 |
| Male (n=64) | | 5 | 83.3 | 8 | 72.7 | 14 | 66.7 | 37 | 59.7 |
| Female (n=36) | | 1 | 16.7 | 3 | 27.3 | 7 | 33. | 25 | 40.3 |
| Hypertension (n=55) | | 5 | 83.3 | 9 | 81.8 | 17 | 80.9 | 24 | 38.7 |
| Diabetes (n=31) | | 4 | 66.7 | 7 | 63.6 | 11 | 52.4 | 9 | 14.5 |
| Current or former smoker (n=65) | | 6 | 100 | 10 | 90.9 | 15 | 71.4 | 34 | 54.8 |
| Hyperlipidemia (n=60) | | 6 | 100 | 10 | 90.9 | 20 | 95.2 | 24 | 38.7 |
| Prior myocardial infarction (n=30) | | 5 | 83.3 | 11 | 100 | 12 | 57.1 | 2 | 3.2 |
| Prior angina (n=25) | | 1 | 16.7 | 0 | 0 | 9 | 42.8 | 15 | 24.2 |
| Prior congestive heart failure (n=17) | | 3 | 50 | 8 | 72.7 | 4 | 19 | 2 | 3.2 |
| Cerebrovascular disease (n=4) | | 2 | 33.3 | 1 | 9.1 | 1 | 4.7 | 0 | 0 |
| Prior bypass surgery (n=2) | | 1 | 16.7 | 0 | 0 | 0 | 0 | 1 | 1.6 |
| Prior angioplasty (n=9) | | 2 | 33.3 | 3 | 27.3 | 0 | 0 | 4 | 6.5 |
| Peripheral vascular disease (n=12) | | 4 | 66.7 | 5 | 45.5 | 2 | 9.5 | 1 | 1.6 |
| Risk factors | No identifiable risk factor | 0 | 0 | 0 | | 2 | 9.5 | 6 | 9.7 |
| | 1 risk factor | 0 | 0 | 1 | 9.1 | 2 | 9.5 | 30 | 48.4 |
| | 2 risk factors | 1 | 16.7 | 3 | 27.3 | 6 | 28.6 | 14 | 22.6 |
| | ≥3 risk factors | 5 | 83.3 | 7 | 63.6 | 11 | 52.4 | 12 | 19.3 |

Gender:

This study had enrolled 64 male and 36 female patients with male to female ratio of 1.78:1. Male sex had been associated with higher frequency of mortality (83.3 % of the died patients, 5 out of 6 patients), new or recurrent myocardial infarction (8 out of 11 patients, 72.7% of those with new or recurrent myocardial infarction), and recurrent ischemia (66.7% of those with recurrent ischemia, 14 out of 21 patients). (see Table-1)

Risk factors:

Being current or former smoker was the most frequent risk factor for unstable angina (65 patients, 65%of the whole sample).

All of the died patients (6 patients) were smoker and had hyperlipidemia.

✓ Prior myocardial infarction had been observed in all of patients with new or recurrent infarction (11 patients, 11% of the whole sample).

✓ Hyperlipidemia had been observed in 95.2% of those with recurrent ischemia (20 out of 21 patients). (see table-1)

This revealed that all of the died patients had combination of 2 or more risk factors (6 patients). Ten out of eleven patients who had new or recurrent myocardial infarction during hospital admission had combination of 2 or more risk factors (90.9% of those with recurrent or new myocardial infarction). Similar risk factors combination had been observed in those with recurrent ischemia (81% of those with recurrent ischemia had 2 or more risk factors). (See table-1). Regarding the classification of unstable angina according to the severity and its effect on the outcome of the patients included in this study, 66.7% of deaths (4 deaths) were observed among class III patients (only 26.3% of class III patients had relieved form chest pain) i.e. angina at rest and acute. 54.5% of those who had recurrent or new myocardial infarction were belong to class III also (6 patients, 31.57% of those with class III). 71% of the improved patients (44 patients) were at class I i.e. new onset, severe or accelerated angina. (see table-2).

Eighty four patients (84% of the whole sample) had primary unstable angina i.e. Class A. 66.7% of deaths (4 deaths) were among those with class C unstable angina i.e. post-infarction unstable angina. (see table-2).

Regarding the intensity of treatment, patients with maximally tolerated doses had worse outcome. 26 out of 27 patients with maximum therapy had adverse events. (see table-2).

Table-2: Patients' distribution according to the severity, the associated clinical circumstances and intensity of treatment

| | All cause mortality (n =6) | | New or recurrent MI (n=11) | | Recurrent ischemia (n=21) | | Improved (n=62) | |
|--|----------------------------|------|----------------------------|------|---------------------------|------|-----------------|------|
| | No. | % | No. | % | No. | % | No. | % |
| Severity | | | | | | | | |
| Class I (new onset, severe or accelerated angina) | 2 | 33.3 | 3 | 27.3 | 10 | 47.6 | 44 | 71 |
| Class II (angina at rest, subacute) | 0 | 0 | 2 | 18.2 | 7 | 33.3 | 13 | 21 |
| Class III (angina at rest, acute) | 4 | 66.7 | 6 | 54.5 | 4 | 19.1 | 5 | 8 |
| Clinical circumstances | | | | | | | | |
| Class A (secondary unstable angina) | 0 | 0 | 0 | 0 | 2 | 9.5 | 3 | 4.8 |
| Class B (primary unstable angina) | 2 | 33.3 | 9 | 81.8 | 14 | 66.7 | 59 | 93.6 |
| Class C (post-infarction unstable angina) | 4 | 66.7 | 2 | 18.2 | 5 | 23.8 | 1 | 1.6 |
| Treatment | | | | | | | | |
| No or minimal treatment | 1 | 16.7 | 0 | 0 | 2 | 9.5 | 47 | 75.8 |
| Symptoms occurring in the setting of standard medical therapy | 1 | 16.7 | 3 | 27.3 | 5 | 23.8 | 14 | 22.6 |
| Symptoms occurring despite maximally tolerated doses of beta blockers, nitrates, and calcium channel blockers | 4 | 66.6 | 8 | 72.7 | 14 | 66.7 | 1 | 1.6 |

Discussion

The diagnosis of unstable angina encompasses a broad spectrum of patients with myocardial ischemia, varying widely in cause, prognosis and responsiveness to therapy. This variability, in addition to the fact that unstable angina is the most frequent cause of admission to coronary care unit, stimulate research workers to make different types of study hoping to reach a point of well understand to the natural history of unstable angina and the risk factors that affect inversely the outcome of such patients, and off course, no one can ignore the importance of this idea in primary prevention of acute myocardial infarction and all of its related complications.

Coronary heart disease is the leading cause of morbidity and mortality among women as well as men all over the world⁽⁸⁾. Women with acute ischemic syndromes tend to be older than men with such syndromes and they have higher rates of associated diabetes and hypertension⁽⁹⁻¹³⁾. Studies report that women who present with acute myocardial infarction have worse in-hospital and long term prognosis than men⁽⁹⁻²¹⁾. In this study, it had revealed that female sex could be regarded as a protective factor against the in-hospital risk of death, recurrent or new myocardial infarction and recurrent ischemia, as being male was associated with higher mortality and short term morbidity (see table-1). This finding is supported by the similar finding of the Global Use of Strategies to Open Occluded Coronary arteries in Acute Coronary Syndromes (GUSTO IIb); a study which found that among patients with unstable angina, female sex was associated with an independent protective effect for infarction or death⁽⁸⁾. This finding could be related to that women who had been included in this study had significantly lower rates of prior myocardial infarction and were less likely ever to have smoked as these two risk factors were the most prominent in increasing the risk of early death and infarction in this study (see below). Only 2 out of the 36 female that were enrolled in this study were current or former smoker (5.5% of the female patients, 3.07% of the smokers included in this study). Furthermore, it had been reported that the impact of smoking on the health status is more pronounced among male than female patients⁽²²⁻²³⁾. In addition, some studies reported that women had less severe and extensive coronary disease and were less likely to undergo revascularization⁽²⁴⁾. This difference in sex incidence of coronary heart disease in general is age dependant in a 12 year follow up of 14, 786 Finnish men and women, age 25-64 found that the incidence of coronary heart disease was three fold higher in men than women, and mortality was five fold higher (this study revealed an incidence of unstable angina among male that was double the observed among female, and mortality of 5 fold higher among men included in this study)⁽²⁵⁾

In this study, All of the deaths due to all cause mortality and most of the recurrent or new myocardial infarction and recurrent ischemia had been observed among those aging 65 year old and older. The importance of age as a factor for study in risk stratification of patients with unstable angina come from the fact that in the western countries like USA and in the industrialized communities, persons over 65 years of age comprise the fastest growing segment of the population. In 1994, there were 33.2 million persons 65 years or older in the United States, nearly 500 000 (1.5%) of whom suffered a myocardial infarction. By the year 2030, there are expected to be over 70 million persons in this age group, accounting for over one million infarctions⁽²⁶⁻²⁷⁾. The anatomic prevalence of coronary heart disease approaches 70% among those who die in their eighth decade⁽²⁸⁾. The coronary involvement is typically more severe and diffuse in the elderly compared to younger patients^(24, 29-30). In addition, elderly patients experienced a much higher incidence of adverse cardiac events both in hospital and by 6 weeks⁽²⁴⁾. Despite the high incidence of anatomic disease, only 10-20% of persons over age of 65 carry a diagnosis of active coronary heart disease. The factors responsible for the discrepancy between the anatomic and the clinical prevalence of disease in the elderly are not well understood. Among the contributing factors are

lack of specific data regarding coronary heart disease in the elderly, misdiagnosed disease, a high prevalence of silent disease, decreased physical activity, and under-treatment of risk factors^(24, 29-30). Therefore, age of 65 year old or older had been regarded as one of the 7 independent predictors for patient's outcome in TIMI risk score and one of the 3 predictors in PRISM-PLUS database using TIMI IIb trial data to identify three criteria, easily obtained at time of admission, that were useful for risk stratification, and included:⁽³¹⁻³²⁾

- 1- Age 65 year old or older.
- 2- ST elevation ≥ 0.05 mm.
- 3- Elevation in serum cardiac markers (serum CK >2 times normal, CK-MB greater than normal, or troponin I or T greater than normal).

In this study risk of developing any of the adverse events during early period of hospitalization among those whose age is 65 year old and more were 65.85%, including all cause mortality, recurrent or new myocardial infarction and recurrent ischemia (27 out of 41 patients belonged to this age group had adverse event).

In this study smoking was the most frequent identified risk factor, 65 patients (65% of the sample) were either current or former smokers. 31 smoker patients (47.7% of the smokers) had adverse events. Hyperlipidemia had just came next to smoking in term of frequency but it carried out higher risk, as 36 out of 60 patients proved to have hyperlipidemia in this study acquired adverse event during the study period (60% of those with hyperlipidemia). The facts regarding the risk of cigarette smoking and cardiovascular disease are well known to both the medical profession and the public⁽³³⁾. Nevertheless many smokers do not believe that smoking is harmful for them. In one study for example, over 60% of 737 current smokers, even those who smoked more than 40 cigarettes per day, did not believe that they were at an increased risk for a myocardial infarction⁽³⁴⁾. Cigarette smoking doubles the risk of developing coronary heart disease and approximately 30% of coronary heart disease deaths are attributable in a dose related manner to smoking. In a study of 106, 745 Korean men, smoking was an independent major risk factor for coronary heart disease, cerebrovascular disease, and total atherosclerotic cardiovascular disease. This harmful effect of smoking was independent of serum cholesterol level and low cholesterol conferred no protective effect⁽³⁵⁾. Furthermore, cigarette smoking increase all cause and cardiovascular mortality⁽³⁶⁻³⁷⁾, and an average smoker dies three years earlier than a non-smoker and a smoker known to be at high risk for coronary heart disease dies 10-15 years earlier than non-smoker⁽³⁸⁻³⁹⁾. In addition patients who continue to smoke after a myocardial infarction have an increased risk of reinfarction and an increased risk of death ranging from 22-47%⁽⁴⁰⁾ (90.9% of those with recurrent or new myocardial infarction included in this study were smokers, 10 out of 11 patients).

Although the serum total cholesterol is the most clearly risk factor for coronary heart disease, many other lipid abnormalities like elevated LDL cholesterol, low HDL cholesterol, or hypertriglyceridemia are associated with increased coronary risk. In this study, 60% of the sample had dyslipidemia. Proof of the pathogenic importance of serum cholesterol has come from randomized trials which showed that reductions in total and LDL-cholesterol levels reduce coronary events and mortality when given for primary prevention as well as secondary prevention in patients with established coronary heart disease⁽⁴¹⁻⁴³⁾. Another important point to be noticed is that the prevalence of dyslipidemia is increased in patients with premature coronary heart disease, as high as 75-85% compared to approximately 40-48% in age matched controls without coronary heart disease⁽⁴⁴⁻⁴⁵⁾.

Hypertension and left ventricular hypertrophy are well established are well established risk factors for adverse cardiovascular outcomes, including coronary heart disease, coronary heart disease mortality, stroke, congestive heart failure, and sudden death⁽⁴⁶⁻⁵⁰⁾. Systolic blood pressure is at least as powerful a coronary risk factor as the diastolic blood pressure and isolated systolic hypertension is now established as a major hazard for coronary heart disease and stroke⁽⁵¹⁻⁵²⁾. In

this study, Hypertension had been associated with 56.4% risk of adverse events. Furthermore, the excess coronary risk associated with hypertension is primarily evident in subgroups with other risk factors or underlying target organ damage and individuals in these subgroups benefit the most from anti-hypertensive therapy, therefore, the Sixth Joint National Committee consider the blood pressure level and the presence or absence of underlying conditions as markers for choosing the suitable therapy for each individual patient⁽⁴⁶⁾.

A classification of unstable angina was proposed by Braunwald in 1989 to facilitate assignment of patients to a particular risk group⁽⁵³⁾. This classification takes into account the severity of symptoms, the clinical circumstances surrounding the anginal episode and the intensity of treatment.

In this study when Braunwald classification had been applied to the patients enrolled in this study, the following points can be concluded:

1- All cause mortality, frequency of new or recurrent myocardial infarction and recurrent ischemia were increased with the increase in the severity class. Class III patients had been associated with the worse outcome. Only 26.3% of those with class III were free from adverse event, compared to 74.6% of those with class I symptoms.

2- According to the clinical circumstances related to unstable angina, secondary unstable angina i.e. class A was the least frequent type (only 5 patients, 5% of the sample). Primary unstable angina i.e. class B was the most frequent type (84 patients, 84% of the sample). With worse outcome noticed among class C (post-myocardial infarction unstable angina). 66.7% of mortality observed among class C patients, only 8.3% of class C patients was free from adverse events (1 patient out of 12).

3- According to the intensity of therapy, the worse outcome had been observed among those patients who are under the maximally tolerated doses of anti-ischemic drugs. 26 out of 27 patients belonging to this group of maximum therapy had been either died (4 patients, 66.6% of deaths), had new or recurrent myocardial infarction (8 patients, 72.7% of those who had recurrent or new myocardial infarction) or had recurrent ischemia (14 patients, 66.7% of those with recurrent ischemia).

These findings mentioned above are agreed with findings of a prospective study of 417 patients that were attempted to identify the incidence and prognosis of different classification groups. It had been shown that after hospital admission recurrence of chest pain increased with severity class (28, 45, and 64 percent for classes I, II, and III). Sixth month infarct free and patient survival were significantly lower for class C (89% and 80%) than for classes A and B patients (97 and 89%). Furthermore, this study found that there were other independent factors that increase the risk of death or worse outcome among patients with unstable angina, a findings that was agreed by the other study conclusions, these factors were mainly older age, male sex, smoking, hypertension and maximal medical therapy⁽⁵⁴⁾.

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